# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

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# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA Serial Number:** | 22-406 |
| **Drug Name:** | XARELTO (rivaroxaban) Film-coated 10 mg tablet for oral intake |
| **Indication(s):** | Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery (10 mg orally, once daily) |
| **Applicant:** | Johnson and Johnson Pharmaceutical Research and Development, LLC |
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# 1. EXECUTIVE SUMMARY

This statistical safety review assesses liver toxicity using data from five randomized, phase 3 trials of rivaroxaban (Rocket, J-Rocket, Einstein DVT, Einstein PE and Einstein Extension). These five trials evaluated chronic use (i.e. treatment durations of >35 days and up to 4 years) of rivaroxaban at doses ranging from 10-30 mg daily in patients with atrial fibrillation, deep venous thrombosis or pulmonary embolism. Assessments of liver toxicity were performed on specific liver function tests using local and central laboratory results and reported hepatic adverse events. A total of 24,134 subjects in the safety populations across the five studies were available for assessment: 12,077 rivaroxaban, 7,764 warfarin, 3,703 enoxaparin, and 590 placebo. Warfarin was used as the active control in both Rocket studies whereas enoxaparin was used in the Einstein DVT and PE studies and placebo in the Extension study.

The proportions of subjects with an elevated alanine aminotransferase (ALT) using predefined clinical thresholds (>3, 5, 8, 10 and 20 times the upper limit of normal (ULN)) were generally balanced between the rivaroxaban and warfarin arms in the pooled Rocket and J-Rocket studies. In the pooled Einstein DVT/PE studies (comprising 31% of data from all five studies), the proportion of patients with an ALT >3x ULN or >5x ULN was significantly lower in the rivaroxaban arm compared to the enoxaparin arm with no difference noted at the higher ALT elevations (Table 1). In the Einstein Extension study (comprising 5% of data from all five studies) the proportion of patients with an ALT>3x ULN was numerically larger in the rivaroxaban arm compared to placebo.

The proportions of subjects with an elevated total bilirubin (TBL) using predefined clinical thresholds (>1.5, 2, 3, 5 and 8x ULN) were generally balanced between treatment groups across all five studies. However, results from the pooled Rocket studies suggested a lower proportion of elevated TBL>1.5 and 2x ULN in the rivaroxaban arm compared to warfarin. In contrast, results from the pooled Einstein DVT/PE studies, resulted in slightly more elevations of TBL>1.5x ULN in the rivaroxaban arm compared to enoxaparin. In the Einstein Extension study, there were no statistically significant differences in the comparisons of TBL elevations between treatment arms.

Models to estimates hazard ratios for high thresholds, e.g. ALT>5x ULN or TBL>3x ULN, may be underpowered to detect any differences between treatment arms due to low event rates by threshold level.

Analysis by study time windows showed that the proportion of patients with ALT>3x ULN and TBL>2x ULN were similar per treatment arm in the Rocket and J-Rocket studies. However, for the Einstein DVT and PE studies there was a large proportion of subjects (77%) who had ALT>3x ULN from baseline up to week 2 in the enoxaparin arm; after week 2, there were more subjects in the rivaroxaban arm (65%) than in the enoxaparin arm (24%) with ALT>3x ULN.

Concurrent (same day) values of ALT>3x ULN and TBL>2x ULN (Hy's Law cases) occurred in approximately 0.5% of subjects (34 and 36 in the rivaroxaban and warfarin groups, respectively) in the pooled Rocket and J-Rocket studies. The average time (standard deviation) from first dose

administration until the occurrence of Hy's Law cases (among the Hy's Law cases only) was longer in the pooled rivaroxaban group [412 (260) days] compared to the warfarin group [329 (206) days] in the Rocket studies. The occurrences of the Hy's Law cases in the rivaroxaban arm were roughly uniform over 2.5 years while those in warfarin occurred mostly within 1 year (78%) post-randomization. The estimated hazard ratio in a time-to-event analysis was 0.95 with a 95% CI of (0.60, 1.52), which suggest no statistically significant difference. However, given the low incidence of Hy's Law cases, the hazard ratios may be underpowered to detect differences between treatment arms. Additional time-to-event analyses considering concurrent and non-concurrent cases, direct bilirubin ≥0.5 TBL, and treatment emergent cases resulted in no statistically significant differences between treatment arms. The numbers of Hy's Law cases in the pooled Einstein studies (follow-up to one-year post-randomization) were 6 and 6 in the rivaroxaban and enoxaparin arms, respectively (approximately less than 0.2% of subjects) and there were no Hy's Law cases observed in the Einstein Extension study (follow-up to one-year after entry into the extension study). These results are summarized in Table 1.

**Table 1: Summary of Laboratory Findings**

| **Studies/Criteria** | **Treatment Arms** | | **HR (R vs Control)** |
|---|---|---|---|
| **Rocket, J-Rocket** | **Rivaroxaban** | **Warfarin** | |
| TBL>1.5x ULN | 512/7,618 (6.72) | 561/7,646 (7.34) | 0.92 (0.81,1.03) |
| TBL>2x ULN | 157/7,618 (2.06) | 201/7,646 (2.63) | **0.79 (0.64,0.97)** |
| Hy's Law Cases | 34/7,618 (0.45) | 36/7,650 (0.47) | 0.95 (0.60,1.52) |
| **Einstein DVT/PE** | **Rivaroxaban** | **Enoxaparin** | |
| ALT>3x ULN | 58/3,556 (1.63) | 111/3,489 (3.18) | **0.50 (0.37,0.69)** |
| ALT>5x ULN | 15/3,556 (0.22) | 33/3,489 (0.95) | **0.44 (0.24,0.81)** |
| TBL>1.5x ULN | 71/3,559 (1.99) | 55/3,491 (1.58) | 1.26 (0.89,1.79) |
| Hy's Law Cases | 6/3,560 (0.17) | 6/3,487 (17) | 0.97 (0.31,3.01) |
| **Einstein Extension** | **Rivaroxaban** | **Enoxaparin** | |
| ALT>3x ULN | 11/591 (1.86) | 3/586 (0.51) | 3.56 (0.99,12.76) |

Hy's Law Cases=ALT>3x ULN and TBL>2x ULN; HR=hazard ratio; R=rivaroxaban
NOTE: HR in bold are statistically significant

For liver assessments of ALT and TBL in the Rocket studies, there was a large proportion of missing data after 1 year (~20%) and 2 years (~56%) in all treatment groups. Subject disposition in the Rocket study showed that there was around 35% early study medication discontinuation mainly due to adverse events and withdrawal of consent. The rate of early study medication discontinuation in the J-Rocket study was approximately 25% and was mostly due to adverse events (11%). Hence although subjects in the Rocket study were followed up to 4 years, most of the laboratory data were available up to 1 year with limited data available out to 2 years post-randomization.

The numbers of reported hepatic adverse events (AEs) were generally balanced across all five studies except for ALT increased, aspartate aminotransferase (AST) increased, cholelithiasis, international normalized ratio (INR) increased, and liver function tests abnormal (based on MedDRA preferred terms (PTs)). In the Rocket study, the proportion of patients with either increased ALT or cholelithiasis was higher in the rivaroxaban arm compared to the warfarin arm. In contrast, the proportions of patients with increased ALT and increased AST were lower in the

rivaroxaban arm compared to the control in the J-Rocket and Einstein DVT/PE studies, respectively; the proportion of patients with increased INR was lower in the rivaroxaban arm compared to control in the Rocket and Einstein DVT/PE studies; and the proportion of patients with abnormal liver function tests was lower in the rivaroxaban arm compared to control in the Einstein DVT study.

The odds ratios (ORs) (95% confidence intervals) for the comparison of rivaroxaban versus active control in the proportion of patients with increased INR was 0.25 (0.20, 0.32) for the pooled Rocket and J-Rocket studies and 0.10 (0.05, 0.20) for the pooled Einstein DVT/PE studies, favoring rivaroxaban. In the pooled Rocket and J-Rocket studies, the time to onset of increased INR (among INR increased subjects only) was shorter in the warfarin arm compared to rivaroxaban (median days of 169 and 577 for warfarin and rivaroxaban, respectively).

There are some inconsistencies in the results from the Rocket and Einstein studies, which might be associated with differences in randomized control treatments (warfarin for Rocket/J-Rocket and enoxaparin for Einstein DVT/PE, placebo for Einstein Extension), treatment durations (up to 2-4 years for Rocket/J-Rocket and 1 year for the Einstein studies), rivaroxaban doses (10-30 mg daily) or study design (double-blind for Rocket and Einstein Extension and open-label for Einstein DVT/PE). In addition, none of the trials evaluated were designed primarily to assess liver toxicity. Note that the pooling of the studies in this review was not pre-specified but a rational for the pooling approach is discussed in section 3.3.4.

In addition, findings from this review are consistent with results presented in an earlier statistical assessment (statistical review by Dr. Chava Zibman) that evaluated serious liver toxicity based on the RECORD 1-4 trials. It is important to note, however, that the dose (10 mg/daily) and duration (up to 35 days) of rivaroxaban studied in the RECORD 1-4 trials was lower and shorter, respectively, compared to the dose and duration of rivaroxaban studied in the Rocket and Einstein studies.

The results of this review are subject to certain interpretation limitations. Please see section 5 for detailed discussion of these issues.

In conclusion, findings from this review suggest that the liver toxicity profile based on assessment of evaluated ALT, TBL, and of reported hepatic events, of rivaroxaban is comparable to active controls, warfarin and enoxaparin, studied across four randomized clinical trials. No notable differences in these outcomes were identified in a single placebo-controlled trial versus rivaroxaban. Lastly, the incidence of Hy's Law cases were similar between the rivaroxaban and warfarin arms in the Rocket trials; however, these events occurred earlier (within the first year) in the warfarin arm compared to the rivaroxaban arm.

# 2. INTRODUCTION

## 2.1 Overview

NDA 22-406 for rivaroxaban (XARELTO) was originally submitted to the Division of Hematology Products (DHP) on July 28, 2008. The proposed indication is for prophylaxis of

deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. The proposed dose is 10 mg for daily oral intake for a recommended duration of 35 and 14 days for hip replacement surgery and knee replacement surgery respectively.

During the original review cycle, a statistical safety review was completed by Dr. Chava Zibman on February 26, 2009 (available in DARRTS) on liver toxicity based on data from the RECORD 1-4 randomized clinical trials submitted in support of the efficacy and safety of rivaroxaban. The safety population of these studies consisted of 6,183 adult patients receiving rivaroxaban and 6,200 receiving enoxaparin as a prophylaxis for DVT and PE following total hip or total knee replacement surgery. The review concluded that a clear liver toxicity signal in rivaroxaban when compared to the randomized active control (enoxaparin) could not be determined. In addition, this review concluded that there was no clear excess of Hy's Law cases in the rivaroxaban arm compared to control.

On May 26, 2009, FDA issued a complete response (CR) letter (available in DARRTS) for NDA 22-406 citing clinical and product quality deficiencies. A clinical deficiency noted was insufficient clinical data to fully characterize a potential risk for serious liver toxicity. The CR letter requested that the applicant provide an assessment of the potential for severe liver toxicity in the applicant's ongoing clinical studies in patients with atrial fibrillation (the "Rocket" studies). The letter further requested information on patients from the ongoing clinical trials with reported elevations of serum ALT values greater than three times ULN and serum total bilirubin (TBL) values greater than twice ULN.

The Rocket studies were included in rivaroxaban NDA (b) (4) submission to the Division of Cardiovascular and Renal Products (DCRP). At the time of this review, NDA (b) (4) was under review for the proposed indication of the prevention of stroke and systemic embolism in subjects with non-valvular atrial fibrillation. (b) (4)

Unlike the RECORD studies (submitted in the original NDA 22-406), which evaluated rivaroxaban for 12 or 35 days, the Rocket studies were chronic dosing studies, i.e. >35 days of planned dosing, with treatment periods of up to 4 years for the Rocket study and up to 2 years for the J-Rocket study. Also, the RECORD studies evaluated rivaroxaban at a lower dose (10 mg daily) for a shorter treatment duration (at most 35 days) while the Rocket studies evaluated rivaroxaban at a higher dose (20 mg daily) for a longer treatment duration (>35 days and up to 4 years).

In response to a consult (received on February 11, 2011) received from DHP, this statistical safety review assessed data from the five rivaroxaban chronic dosing studies included in NDA (b) (4) (and referenced in the complete response for NDA 22-406): Rocket, J-Rocket, Einstein DVT, Einstein PE, and Einstein Extension. These studies were completed phase 3 studies except for Einstein PE which was ongoing at the time of this review. Table 2 provides a summary of the studies and descriptions for each study are as follows:

**Rocket (Study 11630)** was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multi-center, event-driven phase 3 study that compared the efficacy and

safety of rivaroxaban versus warfarin for the prevention of stroke and non-central nervous system (CNS) systemic embolism in subjects with non-valvular atrial fibrillation. This study was conducted in North and Latin America, Europe, and Asia Pacific. Treatment duration was up to 4 years post-randomization.

**J-Rocket (Study 12620)** was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multi-center phase 3 study conducted in Japan that compared the efficacy and safety of rivaroxaban versus warfarin for the prevention of stroke and non-CNS systemic embolism in subjects with non-valvular atrial fibrillation. Treatment duration was up to 2.5 years post-randomization.

**Einstein DVT (Study 11702)** was part of a multi-center, randomized, open-label, assessor-blind, event-driven, non-inferiority program that evaluated the efficacy of rivaroxaban with study treatment durations of 3, 6, or 12 months compared with enoxaparin/Vitamin K anatagonist (VKA) therapy. The program consisted of two independent evaluations: (1) on subjects with confirmed acute symptomatic deep venous thrombosis (DVT) without symptomatic pulmonary embolism (PE) (Einstein DVT) and (2) on subjects with confirmed acute symptomatic PE with or without symptomatic DVT (Einstein PE).

**Einstein Extension (Study 11899)** was a multi-center, randomized, double-blind, placebo-controlled, phase 3, event-driven, superiority study that evaluated the efficacy and safety of once-daily oral Factor Xa inhibitor rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism in subjects with symptomatic deep-vein thrombosis or pulmonary embolism after 6 months of anticoagulant therapy.

**Table 2: Summary of Clinical Studies**

| Study | Proposed Indication (Subject Population) | Rivaroxaban Total Daily Dose | Study Design | Active Control | Scheduled Treatment Duration | Study Population |
|---|---|---|---|---|---|---|
| ROCKET (11630) | Prevention of stroke and non-CNS SE (NVAF) | 20 mg/15 mg[a] | Double-blind, active-controlled | Warfarin* | Up to 4 yrs (exp. 32 mos) | Safety: 14,236 (7,111 R/7,125 W)<br>Rand: 14,269 (7,133 R/7,136 W) |
| J-ROCKET (12620) | Prevention of stroke and non-CNS SE (NVAF) | 15 mg/10 mg[b] | Double-blind, active-controlled | Warfarin* | Up to 2.5 yrs | Safety: 1,278 (639 R/ 639 W)<br>Rand: 1,280 (640 R/ 640 W) |
| EINSTEIN DVT (11702) | Symptomatic DVT without symptomatic PE | 30 mg for 3 wks; then 20 mg | Open label, active-controlled | Enoxaparin (1 mg/kg)/VKA | 3, 6, or 12 months | Safety: 3,429 (1,718 R/1,711 E)<br>Rand: 3,429 (1,718 R/1,711 E) |
| EINSTEIN PE (11702) | Symptomatic PE with or without symptomatic DVT | 30 mg for 3 wks; then 20 mg | Open label, active-controlled | Enoxaparin (1 mg/kg)/VKA | 3, 6, or 12 months | Safety: 4,003 (2,011 R/1,992 E)<br>Rand: 3,997 (2,010 R/1,987 E) |
| EINSTEIN Extension (11899) | DVT/PE after 6 months of anticoagulant therapy | 20 mg | Double-blind, placebo- controlled | Placebo | 6 or 12 months | Safety: 1,188 (598 R/590 P)<br>Rand: 1,197[c] (602 R/ 595 P) |

SE=systemic embolism; NVAF=non-valvular atrial fibrillation; DVT=deep venous thrombosis; PE=pulmonary embolism; VKA=vitamin K antagonist; E=enoxaparin
Rand=all randomized subjects; R=rivaroxaban; W=warfarin; E=enoxaparin; P=placebo
[a]In Rocket, subjects with moderate renal impairment on entry to the study received 15 mg rivaroxaban; [b]In J-Rocket, subjects with moderate renal impairment on entry to the study receive 10 mg rivaroxaban; [c]In Einstein Extension, 632 subjects valid for safety were previously enrolled in the Einstein DVT/PE
*Warfarin doses were titrated to a target INR range of 2.0-3.0, inclusive.

### 2.2 Data Sources

Tabulation and analysis datasets were submitted for the Rocket and J-Rocket studies and only analysis datasets for the Einstein DVT, PE, and Extension studies.

Pooled analysis datasets for both Rocket studies were available for laboratory liver function tests and liver-specific adverse events.

For the Einstein studies, laboratory liver function tests were available but the datasets did not include a variable to indicate the laboratory in which the liver function tests were analyzed (i.e. central or local). A pooled Rocket and Einstein time-to-event dataset (**adttelbp.xpt**) that included a variable for the laboratory in which the sample was assessed was available and considered by the reviewer for analyses. Adverse events datasets were requested by the reviewer and submitted by the sponsor under NDA 22-406 on March 6, 2011.

The clinical study reports and datasets analyzed in this review, including applicant responses to FDA information requests, are located in the CDER Electronic Document Room (EDR) at the links shown below. Note that only the pooled adverse events dataset (adae.xpt) was submitted to NDA 22-406; the laboratory and all other adverse events dataset were submitted to NDA (b) (4)

\\CDSESUB1\EVSPROD\NDA022406
**5.3.5.3 ISS – Integrated Summary of Safety (ISS)** for adverse events analysis dataset for Einstein DVT, Einstein PE, and Einstein Extension studies (**adae.xpt**)

\\CDSESUB1\EVSPROD\NDA202439:
**5.3.5.3 isls - Integrated Summary of Liver Safety (ISLS)** for summary clinical study reports (Rocket, J-Rocket, Einstein DVT, Einstein PE, and Einstein Extension studies), laboratory (**adlbl.xpt**) and adverse events (**adae.xpt**) analysis datasets for Rocket and J-Rocket, and pooled time-to-event analysis datasets (**adttelbp.xpt**) for all five studies.
**5.3.5.4 11702-einstein dvt** for laboratory analysis dataset for Einstein DVT **(liver.xpt**)
**5.3.5.4 11702-einstein pe** for laboratory analysis dataset for Einstein PE (**liver.xpt**)
**5.3.5.4 11899-einstein extension** for laboratory analysis dataset for Einstein Extension (**liver.xpt**)

## 3. STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

Original laboratory values for each liver function test parameter from centers in different regions were reported in varying units. The original laboratory values were converted to standardized values using a documented scheme. However, for the purpose of liver function tests assessments, a derived variable ("RATIO") based on the ratio of the original laboratory value and the ULN of that laboratory value was created and used in the sponsor and reviewer analyses.

The reviewer identified the following data-related issues or limitations:

- For original laboratory values reported with an inequality sign ('<' or '>'), only the numeric portion was used (e.g. for '<0.3 mg/dl', the value 0.3 mg/dl was used) and original values reported with a ',' were converted to '.' (e.g. 34,77 was converted to 34.77). Upon visual inspection of the data, the reviewer did not identify many conversions from the original values with inequality signs or ',' into standardized values for laboratory values of ALT>2x ULN (Note that elevations of *ALT>3x ULN* are of primary interest). That is, most conversions were performed by the sponsor for values of ALT<2x ULN. Furthermore, for those values that were converted, there did not appear to be any bias with regard to treatment assignment i.e. there were as many conversions in the rivaroxaban arm as there were in the active control arms for converted values of ALT>2x ULN.

- In all datasets included in this review, the variable 'TRTP' for 'Planned Treatment' was the only variable available to distinguish treatment groups and was therefore used throughout all analyses in this report. Metadata files state that 'TRTP' represents *actual treatment* for the Einstein DVT, PE and Extension studies, and *planned treatment* for Rocket and J-Rocket studies. If the actual numbers of subjects who were assigned to treatment arms in the Rocket studies are very different from the planned treatment, then the results of the analyses using actual treatment will differ from those provided in this report which was based on planned treatment. ***In summary, the reviewer found it difficult to easily identify a common variable specific to treatment assignment among all available datasets.***

## 3.2 Evaluation of Efficacy

This review focuses only on specific safety parameters measured in phase 3 studies. No assessment of efficacy was performed in this review.

## 3.3 Evaluation of Safety

### 3.3.1 Study Design and Endpoints

**Rocket (Study 11630)** was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multi-center, event-driven phase 3 study that compared the efficacy and safety of rivaroxaban with warfarin for the prevention of stroke and non-CNS systemic embolism in subjects with non-vulvar atrial fibrillation. The primary objective of this study was to demonstrate that the efficacy of rivaroxaban is non-inferior to the efficacy of dose-adjusted warfarin for the prevention of thromboembolic events in subjects with non-valvular AF as measured by the composite of stroke and non-CNS systemic embolism. The principal safety objective of this study was to demonstrate that rivaroxaban is superior to dose-adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.

Eligible subjects included those who had prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or who had at least 2 of the following risk factors: age ≥75 years, hypertension, heart failure and/or left ventricular ejection fraction ≤35%, or diabetes mellitus. Subjects were randomized to one of the following two treatment groups:

- Oral rivaroxaban 20 mg once daily + oral warfarin placebo once daily titrated to a target sham international normalized ratio (INR) of 2.5 (range 2.0-3.0, inclusive). Subjects with moderate renal impairment at screening (defined as calculated creatinine clearance between 30 to 49 mL/min, inclusive) had a dose adaptation to oral rivaroxaban 15 mg once daily.
- Oral warfarin once daily titrated to a target INR of 2.5 (range 2.0-3.0, inclusive) + oral rivaroxaban placebo once daily.

The study was divided into three periods: screening, double-blind treatment (ended with end-of-study/EOS visit), and post-treatment observation (performed approximately 30 days after EOS visit and ended with follow-up visit). Treatment duration per subject depended on the time required to accrue 405 adjudicated primary efficacy endpoint events (stroke, non-CNS systemic embolism in the per protocol population). *Note: The expected maximum duration of the study was 32 months but the protocol permitted it to extend to a maximum of 4 years depending on the rate of subject recruitment and endpoint event rates*.

Study visits for liver function tests occurred at screening, weeks 1, 2, 4 and then every 4 weeks thereafter for the duration of the double-blind treatment period. There were also study visits for treatment discontinuation, EOS, and follow-up (30 days after the last dose of study medication).

Regions that were represented in this trial included North America, Latin America, West Europe (including Israel and South Africa), East Europe, and Asia Pacific (including Australia and New Zealand).

**J-Rocket (Study 12620)** was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multi-center phase 3 study conducted in Japan that compared the efficacy and safety of rivaroxaban with warfarin for the prevention of stroke and non-CNS systemic embolism in subjects with non-valvular atrial fibrillation. The primary objective of this study was to evaluate the safety of rivaroxaban in comparison with that of dose-adjusted warfarin.

Eligible subjects included those who have non-valvular atrial fibrillation and had a prior history of stroke, TIA or non-CNS systemic embolism or had at least 2 of the following risk factors: age ≥75 years, hypertension, heart failure and/or left ventricular ejection fraction ≤35%, or diabetes mellitus. Subjects were randomized to one of the following two treatment groups:

- Rivaroxaban 15 mg once daily or 10 mg once daily for subjects with moderate renal impairment at screening (defined as calculated creatinine clearance between 30 to 49 mL/min, inclusive).
- Warfarin once daily titrated to a target INR range of 1.6-2.6 for subjects ≥70 years old, and 2.0-3.0 for subjects <70 years old.

Study visits for liver function tests occurred at screening, weeks 1, 2, 4 and then every 4 weeks thereafter for the duration of the double-blind treatment period. There were also study visits for treatment discontinuation, EOS, and follow-up (30 days after the last dose of study medication).

**Einstein DVT (Study 11702)** was part of a multi-center randomized, open-label, assessor-blind, event-driven, non-inferiority study to evaluate the efficacy of rivaroxaban with study treatment durations of 3, 6, or 12 months compared with enoxaparin/Vitamin K antagonist (VKA) therapy. There were 2 independent evaluations: (1) in subjects with confirmed acute symptomatic DVT without symptomatic PE (Einstein DVT) and (2) in subjects with confirmed acute symptomatic PE with or without symptomatic DVT (**Einstein PE**).

The designs of the Einstein DVT and Einstein PE studies were almost identical (except that the Einstein PE study had dose confirmation and analysis phases and the Einstein DVT study did not) and the studies were integrated into a single protocol.

Subjects were randomized to one of the following two treatment groups:

- Rivaroxaban 15 mg twice daily for 3 weeks followed by rivaroxaban 20 mg once daily.
- Enoxaparin 1 mg/kg twice daily for at least 5 days in combination with VKA (warfarin or acenocoumarol only) and continued with VKA only when the INR had been ≥2.0 on 2 consecutive measurements at least 24 hours apart.

Study visits for liver function tests occurred at screening, Days 15, 30, 60, 91-98 (Month 3), 178-185 (Month 6), 265-272 (Month 9), 352-359 (Month 12), and follow-up (30 days after the last dose of study medication).

**Einstein Extension (Study 11899)** was a multi-center, randomized, double-blind, placebo-controlled, phase 3, event-driven, superiority study of once-daily oral direct Factor Xa inhibitor rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism in subjects with symptomatic deep-vein thrombosis or pulmonary embolism after 6 months of anticoagulant therapy. The primary efficacy objective was to evaluate whether rivaroxaban was superior to placebo in the long-term prevention of recurrent symptomatic VTE. The study enrolled subjects with symptomatic DVT or PE who either had been treated for 6 or 12 months with VKA or rivaroxaban in the Einstein DVT or Einstein PE studies or who had been treated for 6 to 14 months with VKA (either warfarin or acenocoumarol) in routine clinical practice.

Subjects were randomized to either placebo or rivaroxaban 20 mg once daily for either 6 or 12 months of therapy (decided by investigator prior to randomization).

Study visits for liver function tests occurred at screening, Days 1, 30, 91-98 (Month 3), 178-185 (Month 6), 265-272 (Month 9), 352-359 (Month 12), and follow-up (30 days after the last dose of study medication).

### 3.3.2 Study Populations and Extent of Exposure

A total of 24,172 subjects (12,103 in rivaroxaban, 7,776 in warfarin, 3,698 in enoxaparin, and 595 in placebo) were randomized in the Rocket and Einstein studies, as shown in Table 3. Note that the subjects were pooled according to the active-control arms. The safety population included all randomized subjects who received at least one dose of study drug. However, in the

Einstein PE study, there were 1 and 5 rivaroxaban and enoxaparin subjects, respectively, who received at least one dose of study treatment (i.e. were included in the safety population) but were not randomized: 11702PE-120023014, 11702PE-160173060, 11702PE-160193049, 11702PE-400253004, 11702PE-460063043, and 11702PE-460063044.

***Reviewer's Comment: Adverse events datasets for the Einstein studies were requested by the reviewer and submitted by the sponsor under NDA 22-406 on March 6, 2011. None of the 6 rivaroxaban and enoxaparin subjects who were in the safety population but who were not randomized were in the adverse events datasets submitted by the sponsor.***

**Table 3: Study Populations for Rocket, J-Rocket and Einstein Studies**

| Study | Population | Rivaroxaban | Warfarin | Enoxaparin | Placebo | Total |
|---|---|---|---|---|---|---|
| **Rocket, J-Rocket** | All Rand | 7,773 | 7,776 | - | - | 15,549 |
| | Safety | 7,750 | 7,764 | - | - | 15,514 |
| **Einstein DVT, PE** | All Rand | 3,728 | - | 3,698 | - | 7,426 |
| | Safety* | 3,729 | - | 3,703 | - | 7,432 |
| **Einstein Extension** | All Rand | 602 | - | - | 595 | 1,197 |
| | Safety | 598 | - | - | 590 | 1,188 |
| **Total** | All Rand | 12,103 | 7,776 | 3,698 | 595 | 24,172 |
| | Safety | 12,077 | 7,764 | 3,703 | 590 | 24,134 |

All Rand=all randomized subjects, pooled by active control: warfarin in the Rocket, J-Rocket studies; enoxaparin in the Einstein DVT and PE studies, placebo in the Einstein Extension study
*Six patients (1 in rivaroxaban and 5 in the control) received at least one dose of study drug but were not randomized to study.

Table 4 (copied from Table 2.1-1 of the ISLS) shows the total years of patient exposure for the Rocket and Einstein studies. There are no statistically significant differences in length of exposure between randomized treatment groups within study. These studies spanned from one year up to four years of treatment duration as summarized in Table 2.

**Table 4: Subject Years of Exposure for Rocket, J-Rocket and Einstein Studies**

| Study | Rivaroxaban Years Exposure (No. Subjects) | Comparator Years Exposure (No. Subjects) |
|---|---|---|
| Rocket | 11,140.7 (7,111) | 11,311.4 (7,125) |
| J-Rocket | 872.7 (639) | 841.6 (639) |
| Einstein DVT | 914.4 (1,718) | 881.6 (1,711) |
| Einstein PE | 1,076.9 (2,011) | 1,050.9 (1,992) |
| Einstein Extension | 308.2 (598) | 304.5 (590) |

Table 4 copied from Table 2.1-1 of the ISLS, page 30 (26-month-safety-update-isls.pdf)

In the original NDA 22-406 submission, liver toxicity was also assessed in four clinical studies: RECORD 1, RECORD 2, RECORD 3, and RECORD 4. The numbers of subjects in the safety population for the RECORD studies are summarized in Table 5 (copied from Table 1-2 of the ISS) and the durations of treatment are shown in Table 6 (copied from Table 1-3 of the ISS).

Patient exposure data for the RECORD studies are shown here to summarize the totality of data available to evaluate the liver safety of rivaroxaban for the proposed doses and durations.

The Record studies included over 6,000 subjects per treatment arm who were followed for approximately 12 and 33 days. The dose of rivaroxaban was 10 mg/daily in all four RECORD trials and the enoxaparin dose was 40mg daily in RECORD 1, 2, and 3 and 30mg twice daily in RECORD 4).

**Table 5: Number of Subjects in the Safety Population in Record 1-4 Studies**

| Study | Rivaroxaban | Enoxaparin | Total |
|---|---|---|---|
| RECORD 1 | 2209 | 2224 | 4433 |
| RECORD 2 | 1228 | 1229 | 2457 |
| **Total # hip subjects** | **3437** | **3453** | **6890** |
| RECORD 3 | 1220 | 1239 | 2459 |
| RECORD 4 | 1526 | 1508 | 3034 |
| **Total # knee subjects** | **2746** | **2747** | **5493** |
| **Grand Total** | **6183** | **6200** | **12,383** |

Source: Table 12-1 in Study RECORD 1 (MRR-00233), Study RECORD 2 (MRR-00234); Study RECORD 3 (MRR-00218); and Study RECORD 4 (MRR-A41857).

Table 5 copied from Table 1-2 of the ISS, page 18 (iss-iss-1.pdf)

**Table 6: Duration of Treatment of Active Study Medication by Study in Record 1-4 Studies**

| Study | Rivaroxaban | Enoxaparin |
|---|---|---|
| RECORD 1 | 33.4 ± 6.9 | 33.7 ± 8.2 |
| RECORD 2 | 33.5 ± 6.9 | 12.4 ± 3.0 |
| RECORD 3 | 11.9 ± 2.3 | 12.5 ± 3.0 |
| RECORD 4 | 11.7 ± 2.5 | 11.0 ± 2.4 |

Source: Table 12-1 in Study RECORD 1 (MRR-00233), Study RECORD 2 (MRR-00234); Study RECORD 3 (MRR-00218); and Study RECORD 4 (MRR-A41857).

Table 6 copied from Table 1-3 of the ISS, page 19 (iss-iss-1.pdf)

**Assessment of Missing Laboratory Measures**

For the Rocket and J-Rocket studies, liver function was measured after 2 weeks, 4 weeks, and every 4 weeks until 52 weeks from the start of treatment and then every 12 weeks until the end of treatments, including 30 days after the last administration of study treatment.

Tables 7 and 8 summarize the number of subjects with at least one laboratory observation, each for ALT and TBL, respectively, at Baseline, Week 2, Week 52 (1 year), Week 104 (2 years) and Week 156 (3 years). Tables 7 and 8 show that (1) the number of subjects with ALT and TBL measurements at each visit window are similar between treatment groups and (2) at Week 52 (1 year), only around 80% of subjects in both treatment groups (by study) from baseline have available ALT and TBL measurements; at Week 104 (2 years), only around 44% of all subjects from baseline have available ALT and TBL measurements. These data suggest that, while the proportion of missing data is similar between randomized groups within study, the overall amount of missing data greatly increases between 1 and 2 years follow-up.

**Table 7: ALT Measurements by Study Week in Rocket, J-Rocket and Pooled**

| | Rocket | | J-Rocket | | Pooled | |
|---|---|---|---|---|---|---|
| **Window** | **Rivaroxaban** | **Warfarin** | **Rivaroxaban** | **Warfarin** | **Rivaroxaban** | **Warfarin** |
| Baseline | 7,110 (100) | 7,122 (100) | 639 (100) | 639 (100) | 7,749 (100) | 7,761 (100) |
| 2 | 6,716 (94) | 6,727 (94) | 634 (99) | 638 (100) | 7,350 (95) | 7,365 (95) |
| 52 | 5,548 (78) | 5,628 (79) | 541 (85) | 513 (80) | 6,089 (79) | 6,141 (79) |
| 104 | 3,120 (44) | 3,146 (44) | 197 (31) | 193 (30) | 3,317 (43) | 3,339 (43) |
| 156 | 355 (5) | 365 (5) | 0 (0) | 0 (0) | 355 (5) | 365 (5) |

Note: Windows in Weeks; % based on baseline counts

**Table 8: TBL Data Measurements by Study Week in Rocket, J-Rocket and Pooled**

| | Rocket | | J-Rocket | | Total | |
|---|---|---|---|---|---|---|
| **Window** | **Rivaroxaban** | **Warfarin** | **Rivaroxaban** | **Warfarin** | **Rivaroxaban** | **Warfarin** |
| Baseline | 7110 (100) | 7122 (100) | 639 (100) | 639 (100) | 7749 (100) | 7761 (100) |
| 2 | 6,716 (94) | 6,726 (94) | 636 (100) | 638 (100) | 7,352 (95) | 7,364 (95) |
| 52 | 5,546 (78) | 5,629 (79) | 541 (85) | 513 (80) | 6,087 (79) | 6,142 (79) |
| 104 | 3,117 (44) | 3,147 (44) | 197 (31) | 193 (30) | 3,314 (43) | 3,340 (43) |
| 156 | 355 (5) | 365 (5) | 0 (0) | 0 (0) | 355 (5) | 365 (5) |

Note: Windows in Weeks; % based on baseline counts

Table 9 (copied from Table 7 in the CSR) summarizes the patient disposition for the Rocket study. The table shows that approximately 65% of subjects in the safety population in each treatment arm completed the double-blind treatment period and entered the 30-day post-treatment observation follow-up period. The most common reasons for premature treatment discontinuation were adverse events (13%) or withdrawal of consent (9%). There does not appear to be any imbalances in the reasons for premature treatment discontinuation between treatment groups. For the J-Rocket study, the completion rate was approximately 75% and treatment discontinuation was mainly due to adverse events (11%) (results are not shown).

**Table 9: Study Medication Completion/Withdrawal Information During the Double-Blind Period (Rocket Study)**

(Study 39039039AFL3001: Safety Analysis Set)

| Status<br>Discontinuation Reason | Rivaroxaban (N=7111)<br>n (%) | Warfarin (N=7125)<br>n (%) | Total (N=14236)<br>n (%) |
|---|---|---|---|
| **Completed Study Medication** | 4591 (64.56) | 4657 (65.36) | 9248 (64.96) |
| **Early Study Medication Discontinuation** | 2520 (35.44) | 2468 (34.64) | 4988 (35.04) |
| Adverse Event | 993 (13.96) | 919 (12.90) | 1912 (13.43) |
| -Bleeding | 304 ( 4.28) | 219 ( 3.07) | 523 ( 3.67) |
| -Non-Bleeding | 689 ( 9.69) | 699 ( 9.81) | 1388 ( 9.75) |
| -Missing/Incomplete Data | 0 | 1 ( 0.01) | 1 ( 0.01) |
| Non-Compliant with Study Medication | 134 ( 1.88) | 164 ( 2.30) | 298 ( 2.09) |
| Consent Withdrawn | 671 ( 9.44) | 673 ( 9.45) | 1344 ( 9.44) |
| Investigator Decision, Not Protocol Related | 191 ( 2.69) | 178 ( 2.50) | 369 ( 2.59) |
| Lost to Follow-Up | 6 ( 0.08) | 8 ( 0.11) | 14 ( 0.10) |
| Protocol Violation | 142 ( 2.00) | 124 ( 1.74) | 266 ( 1.87) |
| Clinical Efficacy Endpoint Reached | 300 ( 4.22) | 332 ( 4.66) | 632 ( 4.44) |
| Study Terminated by Sponsor | 82 ( 1.15) | 69 ( 0.97) | 151 ( 1.06) |
| Missing/Incomplete Data | 1 ( 0.01) | 1 ( 0.01) | 2 ( 0.01) |

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Adverse event is based on the STUDY DRUG COMPLIANCE CRF page
Note: Completed study medication: a subject's last dose date is greater than or equal to the site notification date.
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Copied from Table 7 in the CSR, page 108

### 3.3.3 Demographic and Baseline Characteristics

Table 10 summarizes demographic and baseline characteristics of subjects randomized in the five studies. Table 10 shows that subjects ranged in age from 18-97 years with mean (standard deviation) of 71 (9) and 57 (17) years in the pooled Rocket and Einstein studies respectively. There were generally more males (55-60%) than females (40-45%) and the most represented race was White (70-78%) followed by Asian (8-20%) overall.

**Table 10: Demographic and Baseline Characteristics (All Randomized Subjects)**

| | Rivaroxaban | Warfarin | Enoxaparin | Total |
|---|---|---|---|---|
| **Rocket, J-Rocket** | **N=7,773** | **N=7,776** | **-** | **N=15,549** |
| Age at baseline (years) | MN (SD): 71 (9)<br>MD (R):73 (25-97) | MN (SD): 71 (9)<br>MD (R):73 (28-95) | - | MN (SD): 71 (9)<br>MD (R):73 (25-97) |
| Sex | M: 4,832 (62)<br>F: 2,941 (38) | M: 4,804 (62)<br>F: 2,972 (38) | - | M: 9,636 (62)<br>F: 5,913 (38) |
| Race* | W: 5,924 (76)<br>A: 1,537 (20)<br>O: 312 (4) | W: 5,960 (77)<br>A: 1,529 (20)<br>O: 287 (3) | - | W: 11,884 (76)<br>A: 3,066 (20)<br>O: 599 (4) |
| **Einstein DVT, PE** | **N=3,724** | **-** | **N=3,689** | **N=7,435** |
| Age at baseline (years) | MN (SD): 57 (17)<br>MD (R): 58 (18-97) | - | MN (SD): 57 (17)<br>MD (R): 58 (18-97) | MN (SD): 57 (17)<br>MD (R): 58 (18-97) |
| Sex | M: 2,070 (56)<br>F: 1,654 (44) | - | M: 1,980 (54)<br>F: 1,709 (46) | M: 4,050 (55)<br>F:3,363 (45) |
| Race* | W: 2,636 (71)<br>A: 354 (10)<br>O: 738 (19) | - | W: 2,611 (71)<br>A: 340 (9)<br>O: 747 (20) | W: 5,247 (71)<br>A: 694 (9)<br>O: 1,485 (20) |
| | **Rivaroxaban** | **Placebo** | | |
| **Einstein Extension** | **N=602** | **N=595** | | **N=1,197** |
| Age at baseline (years) | MN (SD): 58 (16)<br>MD (R): 60 (18-89) | MN (SD): 58 (16)<br>MD (R): 59 (19-96) | - | MN (SD): 58 (16)<br>MD (R): 59 (18-96) |
| Sex | M: 354 (59)<br>F: 248 (41) | M: 340 (57)<br>F: 255 (43) | - | M: 694 (58)<br>F: 503 (42) |
| Race* | W: 467 (78)<br>A: 47 (8)<br>O: 88 (14) | W: 462 (78)<br>A: 48 (8)<br>O: 85 (14) | - | W: 929 (78)<br>A: 95 (8)<br>O: 173 (14) |

MN (SD)=mean (standard deviation); MD (R)=median (min-max);
Race*: W=White; A=Asian; O=Other race (Black, American Indian or Alaskan native, native Hawaiian or other Pacific islander, other)

### 3.3.4 Endpoints and Statistical Methodologies

**Pooled Analyses**

The applicant included results from pooled analyses of the following trials:

(1) Rocket and J-Rocket
(2) Einstein DVT, Einstein PE, Einstein Extension, and other phase 2 studies (ODIXa-DVT/Study 11223 and Einstein/Study 11528)
(3) All available studies (Rocket studies, Einstein phase 2 and 3 studies, ODIXa-DVT/Study 11223, and Atlas ACS TIMI 46/Study 11898).

The reviewer only considered pooling of the phase 3 randomized clinical trials (i.e. the review did not include the ODIXa-DVT/Study 11223 and Atlas ACS TIMI 46/Study 11898 and the sponsor's results from these analyses are not discussed). Analyses were based on pooled data from the following studies:

(1) Rocket and J-Rocket
(2) Einstein DVT and Einstein PE

The pooling of these studies was not pre-specified but the rationale for this approach was based on the similarity of treatment indications (atrial fibrillation for Rocket and J-Rocket), active comparators (warfarin for Rocket and J-Rocket; enoxaparin for Einstein DVT and Einstein PE) and study duration (more than 1 year for Rocket and J-Rocket; up to a year for Einstein DVT and Einstein PE). The Einstein Extension study was analyzed separately because it included a placebo control and no active comparator.

**Scope of Review**

The sponsor's assessment of liver safety involved analyses of (a) laboratory hepatic tests (b) reports of hepatic disorder adverse events, and (c) independent assessments made by external DILI expert evaluations on a subset of the safety data related to possible liver injury. This statistical safety review only covers the analyses of laboratory hepatic tests and of reports of hepatic disorder adverse events.

## (a) Laboratory Hepatic Tests

The specific laboratory parameters of interest are ALT and TBL. Thresholds of ALT >3x, 5x, 8x, 10x, and 20x the ULN and TBL >1.5x, 2x, 3x, 5x, and 8x the ULN were pre-specified. Joint elevations of ALT>3x ULN and TBL>2x ULN are considered as Hy's Law cases and represent an increased risk of liver failure. Joint elevations of ALT>3x ULN and TBL>2x ULN were classified as either ***concurrent*** (occurred on same day) or ***non-concurrent*** (occurred on different calendar days).

The applicant's primary analysis focused on post-baseline (occurring after the first study drug administration) cases that were expected to represent drug-induced liver injury (DILI): either concurrent cases or cases where the ALT elevation occurred first followed by the TBL elevation within 30 days. A ratio of direct to total bilirubin of at least 50% was also used to identify potential DILI cases. Specimens of AST and alkaline phosphatase (AP) were collected only if ALT was >3x ULN. Limited analysis was performed on AST.
**Post baseline** was defined as any assessment after the first study medication date for subjects with non-missing post baseline values (regardless of discontinuation of study medication during the entire study). **Treatment emergent** was defined as from the first to last study medication date plus 2 days for subjects with normal baseline values and non-missing post baseline values.

The absolute differences of percentages and hazard ratios between rivaroxaban and comparator treatment groups were calculated for the ALT and TBL thresholds. Assessments were made on post-baseline abnormalities defined as occurring after the first dose of any study drug, regardless of time of event onset relative to the last dose of study drug as well as treatment emergent abnormalities defined as occurring after the first dose and up to 2 days after the last dose of study drug. Kaplan-Meier plots were provided for the cumulative first incidence of the laboratory abnormalities.

**(b) Hepatic Disorder Adverse Events**

The applicant identified hepatic disorder adverse events of interest using Medical Dictionary of Regulatory Affairs (MedDRA) Maintenance and Support Services Organization (MSSO) standardized medical queries (SMQ). Analyses were focused on the Hepatic Disorders SMQ excluding only the Liver related coagulation and bleeding disturbances subsearch SMQ and on the Hepatic Disorders SMQ excluding both, the Liver related coagulation and bleeding disturbances subsearch SMQ and the Liver related investigations, signs and symptoms subsearch SMQ. A broader search strategy was also implemented using additional key words for serious hepatic disorder adverse events not capture by the Hepatic Disorders SMQ.

Only hepatic disorder adverse events reported after the first dose of any study drug were considered in the analyses (defined as **post-baseline event**). An adverse event was considered **treatment emergent** if it occurred after the first dose and up to 2 days after the last dose of study drug.

Summary tables per treatment group, including absolute differences in incidences, were provided for hepatic disorder adverse events, serious adverse events, adverse events leading to permanent study drug discontinuation, adverse events with an outcome of death and study drug related adverse events.

Incidences of adverse events were given by MedDRA System Organ Class (SOC) and Preferred Term (PT) for each SMQ classification.

Adverse events in the Rocket, Einstein DVT and Einstein PE studies were coded using MedDRA 13.0 while those in the J-Rocket and Einstein Extension studies were coded using MedDRA 12.1 and MedDRA 12.0, respectively.

***Reviewer's Comment: It is possible that the PTs varied by MedDRA version. In the pooled analysis, the sponsor chose to use one version when searching for events. While this approach was not justified in the study report, it is likely that the differences in coding dictionaries have minimal impact on the evaluation of liver safety across studies.***

### 3.3.5 Applicant's Results and Statistical Safety Reviewer's Findings and Comments

**(a) Liver Function Tests (Laboratory Values)**

Laboratory values for liver function tests, coded as (1) central or (2) central and local, were available for the Rocket, Einstein DVT, Einstein PE, and Einstein Extension studies while only the local laboratory values were available for the J-Rocket study. In (1) values were reported from central laboratories only while in (2), values were reported from either central or local (or both) laboratories.

Table 11 summarizes the results of the measures of ALT based on central laboratory reading only for Rocket, Einstein DVT, Einstein PE, and Einstein Extension studies, and local laboratory

for the J-Rocket study. The table shows that the proportions of subjects with ALT values within specific categories are less than 3% of all available laboratory values reported for the pooled Rocket and J-Rocket studies. The proportions of subjects with liver function tests in specific categories were generally balanced between the treatment arms in pooled comparisons except for the Einstein DVT and Einstein PE studies, where the proportions were lower in the rivaroxaban arm compared to control for the >3x and >5x ULN thresholds with 95% hazard ratio confidence interval (CI) excluding one.

**Table 11: ALT (SGPT) Post Baseline Data***

| Study/Criteria | Rivaroxaban | Warfarin | HR (R vs Control) |
|---|---|---|---|
| Rocket, J-Rocket | Obs=7,618 (%) | Obs=7,646 (%) | |
| >3x ULN | 217 (2.85) | 217 (2.84) | 1.01 (0.84,1.22) |
| >5x ULN | 81 (1.06) | 71 (0.93) | 1.15 (0.84,1.58) |
| >8x ULN | 33 (0.43) | 29 (0.38) | 1.15 (0.70,1.89) |
| >10x ULN | 19 (0.25) | 21 (0.27) | 0.91 (0.49,1.70) |
| >20x ULN | 3 (0.04) | 4 (0.05) | - |
| | **Rivaroxaban** | **Enoxaparin** | |
| Einstein DVT/PE | Obs=3,556 (%) | Obs=3,489 (%) | |
| >3x ULN | 58 (1.63) | 111 (3.18) | **0.50 (0.37,0.69)** |
| >5x ULN | 15 (0.22) | 33 (0.95) | **0.44 (0.24,0.81)** |
| >8x ULN | 8 (0.14) | 9 (0.26) | 0.86 (0.33,2.24) |
| >10x ULN | 5 (0.00) | 5 (0.14) | 0.97 (0.28,3.35) |
| >20x ULN | 0 (0.00) | 0 (0.00) | - |
| | **Rivaroxaban** | **Placebo** | |
| Einstein Extension | Obs=591 (%) | Obs=586 (%) | |
| >3x ULN | 11 (1.86) | 3 (0.51) | 3.56 (0.99,12.76) |
| >5x ULN | 2 (0.34) | 1 (0.17) | - |
| >8x ULN | 1 (0.17) | 0 (0.00) | - |
| >10x ULN | 1 (0.17) | 0 (0.00) | - |
| >20x ULN | 0 (0.00) | 0 (0.00) | - |

*For subjects who received at least one dose of study medication (in safety population), includes all study data since the date of the first double-blind study medication administration;
Obs=Number of non-missing laboratory values
Note: Einstein PE is ongoing at time of review
Note: HR=hazard ratio was not computed when the total number of events is at least 10 with at least 1 event in one treatment arm.
Note: The numbers in columns 2 and 3 in Table 12 for the Einstein studies were obtained using the time-to-event analysis dataset (adttelbp.xpt) instead of the laboratory values (liver.xpt) since only the adttelbp.xpt dataset included a variable for the laboratory source.

***Reviewer's Comment: The event rates of ALT thresholds other than ALT>3x ULN are considerably low. Comparisons within level are likely underpowered to detect a statistically significant differences using the Cox model.***

ALT laboratory values for the Rocket study classified as "central and local" were also reviewed. The proportions of subjects with specific categories of ALT levels, although slightly different from those provided in Table 11, were generally balanced between the treatment arms and none of the CI's for the hazard ratios included 1, suggesting that the time to ALT elevations were

balanced between treatment arms (results not shown). However, the comparisons are also likely underpowered to detect an increase in HR for higher thresholds.

Table 12 summarizes the TBL results using laboratory values classified as "central" for the Rocket, Einstein DVT, Einstein PE, and Einstein Extension studies, and local laboratory values for the J-Rocket study. The table shows that the proportions of subjects with specific categories of TBL levels (i.e. >1.5x ULN, etc.) are around 7% of all available laboratory data for the pooled Rocket and J-Rocket studies and generally balanced between the treatment arms except for the Rocket and J-Rocket studies, where the proportion of subjects with elevated TBL was smaller in the rivaroxaban arm compared to the control for the >1.5x and >2x ULN thresholds.

**Table 12: Total Bilirubin (based on central laboratory) Post-Baseline Data**

| Study/Criteria | Rivaroxaban | Warfarin | HR (R vs Control) |
|---|---|---|---|
| Rocket, J-Rocket | Obs=7,618 (%) | Obs=7,646 (%) | |
| >1.5x ULN | 512 (6.72) | 561 (7.34) | 0.92 (0.81,1.03) |
| >2x ULN | 157 (2.06) | 201 (2.63) | **0.79 (0.64,0.97)** |
| >3x ULN | 32 (0.42) | 33 (0.43) | 0.98 (0.60,1.59) |
| >5x ULN | 4 (0.05) | 9 (0.12) | 0.45 (0.14,1.45) |
| >8x ULN | 1 (0.01) | 4 (0.05) | - |
| | **Rivaroxaban** | **Enoxaparin** | |
| Einstein DVT, PE | Obs=3,559 (%) | Obs=3,491 (%) | |
| >1.5x ULN | 71 (1.99) | 55 (1.58) | 1.26 (0.89,1.79) |
| >2x ULN | 27 (0.76) | 22 (0.63) | 1.20 (0.68,2.09) |
| >3x ULN | 4 (0.11) | 9 (0.26) | 0.43 (0.13,1.40) |
| >5x ULN | 3 (0.08) | 4 (0.11) | - |
| >8x ULN | 2 (0.06) | 2 (0.06) | - |
| | **Rivaroxaban** | **Placebo** | |
| Einstein Extension | Obs=590 (%) | Obs=586 (%) | |
| >1.5x ULN | 11 (1.86) | 8 (1.37) | 1.38 (0.56,3.44) |
| >2x ULN | 2 (0.34) | 5 (0.85) | - |
| >3x ULN | 0 (0.00) | 0 (0.00) | - |
| >5x ULN | 0 (0.00) | 0 (0.00) | - |
| >8x ULN | 0 (0.00) | 0 (0.00) | - |

*For subjects who received at least one dose of study medication (in safety population), includes all study data since the date of the first double-blind study medication administration;
Obs=Number of non-missing laboratory values
Note: Numbers in parenthesis in the 2nd/3rd colums are percentages of number of subjects over Obs.
Note: Einstein PE was ongoing at the time of data submission
Note: HR=hazard ratio was not computed when the total number of events is at least 10 with at least 1 event in one treatment arm.

***Reviewer's Comment: The event rates of TBL thresholds other than TBL>1.5x and TBL>2x ULN are considerably low. Comparisons within level are likely underpowered to detect a statistically significant differences using the Cox model.***

TBL laboratory values that were classified as "central and local" were also available for the Rocket study. The proportions of subjects with specific categories of TBL levels, although slightly different from those in Table 12, were generally balanced between the treatment arms

(data not presented). There were two exceptions, which were for the criteria >2x ULN [206 (2.7%) rivaroxaban vs. 258 (3.4%) warfarin] and >8x ULN [8 (0.1%) rivaroxaban vs. 19 (0.2%) warfarin]. Although the proportions differ from those in Table 12 at the same TBL level, the degree and direction of imbalance between treatment arms are similar.

The applicant provided a scatter plot, (shown below in Figure 1-copied from Figure 2.1-3 of afib-isls-01.pdf), of the post-baseline maximum ALT levels versus maximum TBL level (based on central and local laboratory assessment) at any time (i.e. not necessarily on the same day) in the pooled Rocket and J-Rocket studies. Figure 1 shows the distribution of ALT and TBL for all subjects including 43 subjects per treatment arm (upper right-hand quadrant) that were considered Hy's Law cases. These 43 subjects constitute approximately 0.55% of the total safety populations in each treatment arm. There were slightly more subjects in the warfarin arm (solid circle) compared to the rivaroxaban arm (open circle) with elevated ALT (>3xULN) or TBL (>2xULN); however, the majority of the subjects in the safety population (95% rivaroxaban and 94% warfarin) did not have elevated ALTs or TBLs.

**Figure 1: Scatter Plot of Baseline and Postbaseline Maximum ALT Levels with Maximum Total Bilirubin Levels (Based on Central and Local laboratory assessment) Rocket and J-Rocket: Safety Analysis Set**

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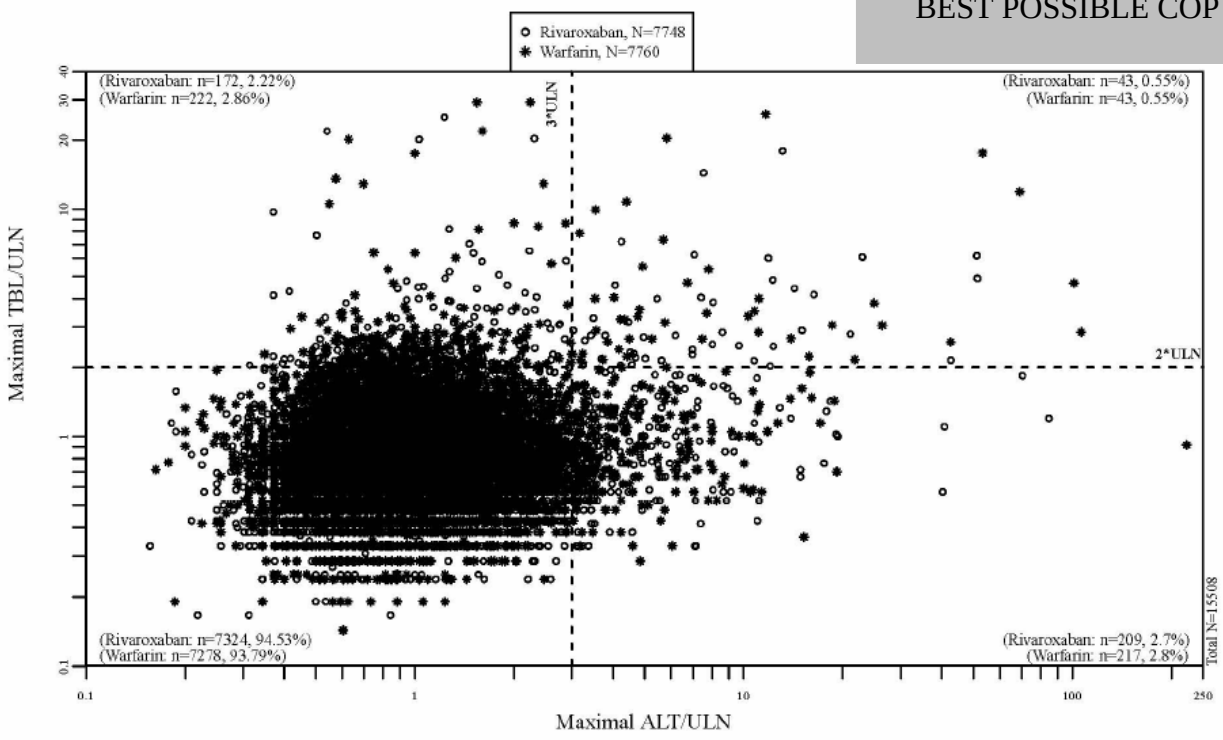


Figure 1 copied from Figure 2.1-3 of afib-isls-01.pdf, page 43, data from pooled Rocket and J-Rocket trials, post-baseline maximum ALT levels versus maximum TBL level (based on central and local laboratory assessment) at any time after first dose (concurrent and non-concurrent)

The applicant also included time-to-event analyses for the Hy's Law cases reported in the Rocket and J-Rocket studies under various clinical scenarios including concurrent and non-concurrent, direct bilirubin ≥0.5 TBL, and treatment emergent cases. Results are summarized in Table 13

(copied from Figure 2.1-6 of afib-isls-01.pdf). None of these analyses yielded statistically significant differences between the treatment arms.

**Table 13: Incidence of Prespecified Laboratory Abnormalities with Hazard Ratios (Combined ALT>3xULN and TBL>2xULN) (Based on Central and Local laboratory assessments) Rocket and J-Rocket: Safety Analysis Set**

| Lab Test | Rivaroxaban (N=7750) n/J(%) | Comparators(a) (N=7764) n/J(%) | HR Rivaroxaban to Comparators(a) (95% CI) | Quantitative Interaction p-value | Qualitative Interaction p-value |
|---|---|---|---|---|---|
| Concurrent Cases on Same Day | | | | | |
| POST BASELINE | | | | | |
| ALT > 3xULN and TBL > 2xULN | 34/7618(0.45) | 36/7650(0.47) | 0.95(0.60,1.52) | 0.982 | |
| ALT > 3xULN and TBL > 2xULN with BILIDIR ≥ 0.5 TBL | 16/7613(0.21) | 22/7638(0.29) | 0.73(0.38,1.40) | 0.706 | |
| TREATMENT EMERGENT | | | | | |
| ALT > 3xULN and TBL > 2xULN | 26/7487(0.35) | 23/7578(0.30) | 1.15(0.65,2.01) | 0.857 | |
| ALT > 3xULN and TBL > 2xULN with BILIDIR ≥ 0.5 TBL | 11/7483(0.15) | 15/7571(0.20) | 0.74(0.34,1.61) | 0.775 | |
| Non-concurrent Cases on Different Days | | | | | |
| POST BASELINE | | | | | |
| ALT > 3xULN Followed by TBL > 2xULN Within 30 Days | 22/7618(0.29) | 25/7650(0.33) | 0.89(0.50,1.58) | 0.360 | |
| ALT > 3xULN Followed by TBL > 2xULN Within 30 Days and BILIDIR ≥ 0.5 TBL | 10/7613(0.13) | 11/7638(0.14) | 0.92(0.39,2.16) | 0.576 | |

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(a) Comparators: WARFARIN
Note: ULN = Upper Limit of Normal Range; TBL: TOTAL BILIRUBIN; BILIDIR: DIRECT BILIRUBIN; N= # of subjects valid for safety population; n = Number of subjects with events; J= Number of subjects with non-missing ALT and TBL lab values for concurrent and/or non-concurrent cases for each time period
Note: 'Concurrent cases-On Same Day' refers to the cases (ALT >3x ULN and TBL >2x ULN) occurring on the same calendar day. For multiple values observed on the same calendar day, the max value is used for the day. 'Non-concurrent cases On Different Days' refers to the cases (ALT>3xULN and TBL>2xULN) occurring on different calendar days. If subjects had (ALT>3x ULN and TBL >2x ULN) occurring on the same days and different days as well, they are counted in both 'Concurrent cases-On Same Day' category and 'Non-concurrent cases On Different Days' category
Note: POST BASELINE: After the first study medication date for subjects with non-missing post baseline values
Note: TREATMENT EMERGENT: From the first to last study medication date plus 2 days for subjects with normal baseline values and non-missing post baseline values
Note: Hazard Ratio (95% CI): time to event analysis of the first ALT>3xULN and TBL>2xULN using a Cox model stratified by study with treatment as the covariate. Hazard ratio will be provided when the total number of events is 10 or more for the two treatment groups combined and at least 1 event occurs in each group.
Note: Quantitative interaction will be measured using a Wald test; and if significant ($p \leq 0.05$) qualitative interaction will be measured using a Gail-Simon test. Source: Table ISLS1.4 in Appendix 9.1.1.

[illegible] and J-ROCKET: Safety Analysis Set

| Lab Test | Rivaroxaban (N=7750) n/J(%) | Comparators(a) (N=7764) n/J(%) | HR Rivaroxaban to Comparators(a) (95% CI) | Quantitative Interaction p-value | Qualitative Interaction p-value |
|---|---|---|---|---|---|
| Concurrent and Non-concurrent Cases | | | | | |
| POST BASELINE | | | | | |
| ALT > 3xULN and TBL > 2xULN Either on the Same Day or Within the Following 30 Days | 36/7618(0.47) | 38/7650(0.50) | 0.96(0.61,1.51) | 0.986 | |
| ALT > 3xULN and TBL > 2xULN Either on the Same Day or Within the Following 30 Days and with BILIDIR ≥ 0.5 TBL | 18/7613(0.24) | 23/7638(0.30) | 0.79(0.43,1.46) | 0.782 | |

See footnotes on the first page of the table.
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Table copied from Figure 2.1-6 of afib-isls-01.pdf, page 43

A summary of the hazard ratios for the time from the first study drug administration to the first post-baseline occurrence of Hy's Law cases ***either on the same day or within 30 days*** (concurrent and non-concurrent cases) for all studies is shown in Figure 2 (copied from Figure 2.1-4 of afib-isls-01.pdf; reviewed studies are enclosed in red-line boxes - reviewer added). The figure illustrates no difference between treatment groups with 95% CI hazard ratios including one. Note: The number of Hy's Law cases for pooled Rocket and J-Rocket in Figure 2 differ from those presented in Figure 1 due to the different time period in which

**Figure 2: Hazard Ratios and 95% CIs for the Time from the First Study Drug Administration to the First Post-baseline Occurrence of Hy's Law Cases Either on the Same Day or Within 30 Days (Based on Central and Local laboratory assessments)**

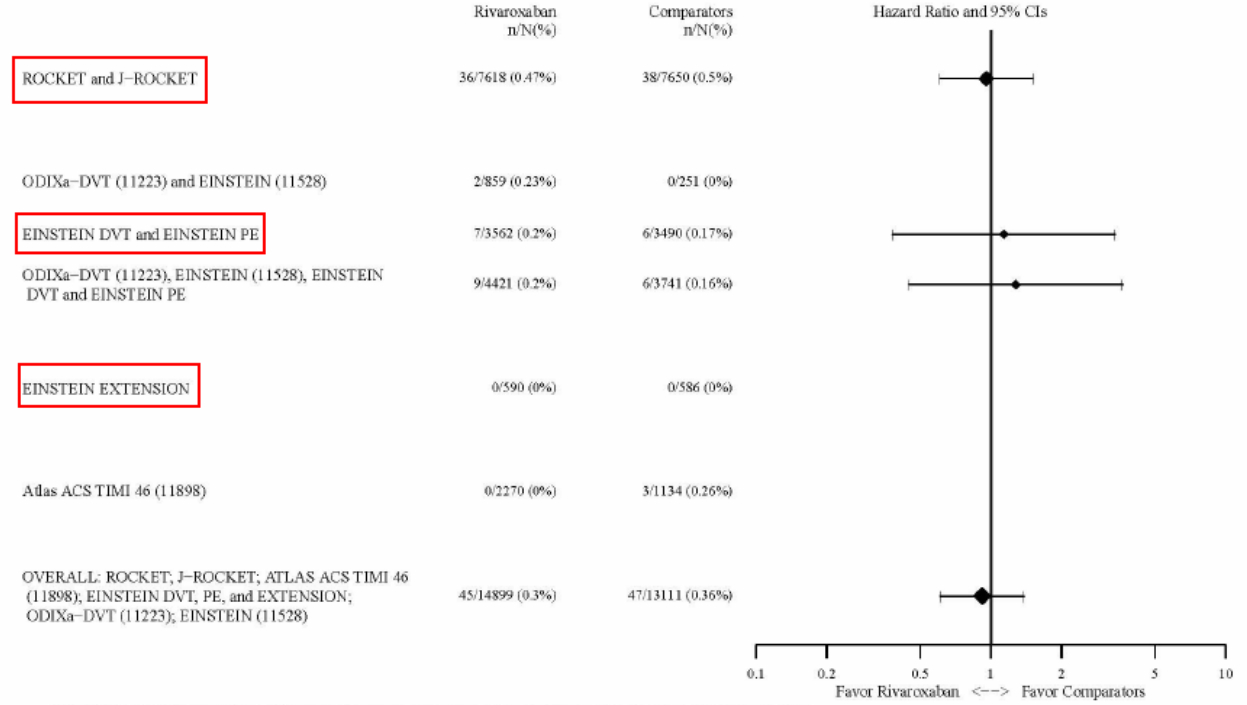


Figure copied from Figure 2.1-4 of afib-isls-01.pdf, page 51
Reviewed studies are enclosed in red-line boxes (reviewer added), analysis based central and local laboratory assessment from data in the safety analysis set

***Reviewer Comment: The event rates for the Hy's Law cases in each treatment arm are low (~0.5%). The hazard ratios calculated using the Cox model may not have enough power to detect a difference if it exists.***

## Reviewer Additional Analyses of Elevated ALT and Assessment of Hy's Law Cases

The reviewer conducted further analyses on the proportion of subjects with elevated ALT. For each peak ALT>3x ULN in all subjects, the corresponding TBL ***measured on the same day*** as the ALT were analyzed using local, central, and serious adverse event laboratory values for Rocket and local laboratory values for J-Rocket (results summarized in Table 14). *Note: The liver tests laboratory datasets for the Einstein DVT, Einstein PE and Einstein Extension studies did not include a variable for the laboratory source therefore, it is unclear if values are based on local or central laboratory readings.*

In the pooled Rocket and J-Rocket studies, there were 238 rivaroxaban and 244 warfarin subjects with ALT>3x ULN and corresponding TBL measured on the same day as the ALT; in the pooled Einstein DVT and PE, there were 67 rivaroxaban and 123 warfarin subjects in the same scenario.

Table 14 shows that the proportion of these events in the treatment arms is balanced and most TBL values fall into the <1.5x ULN level.

In the pooled Rocket and J-Rocket data set, there were 34 and 36 subjects in the rivaroxaban and warfarin arms, respectively, that met the criteria for Hy's Law cases (i.e. ALT>3xULN and TBL>2xULN, outlines in red box in table). *The reviewer was therefore able to replicate the applicant's finding summarized above in Table 13.* Among the Hy's Law cases only, the average time (standard deviation) from first dose administration until the occurrence of the Hy's Law cases was longer in the rivaroxaban arm [412 (260) days] compared to the warfarin arm [329 (206) days]. In a time-to-event analysis that also considers censored observations, the estimated hazard ratio (95% CI) was 0.95 (0.60, 1.52). *Note: There was one subject (study id='12620-007949-200020008') whose ALT was 4.42 >3x ULN and* ***TBL=2.00*** *in the warfarin arm.*

**Table 14: Total Bilirubin Post-Baseline Data Corresponding to ALT>3xULN**

| Study/Criteria | Rivaroxaban | Warfarin |
|---|---|---|
| **Rocket, J-Rocket** | Obs=7,618 (%) | Obs=7,646 (%) |
| =<1.5x ULN | 191 (2.51) | 197 (2.58) |
| >1.5x ULN | 47 (0.62) | 47 (0.61) |
| >2x ULN | 34 (0.45) | 36 (0.47) |
| >3x ULN | 16 (0.21) | 20 (0.26) |
| >5x ULN | 5 (0.07) | 7 (0.09) |
| >8x ULN | 2 (0.03) | 3 (0.04) |
| | **Rivaroxaban** | **Enoxaparin** |
| **Einstein DVT, PE** | Obs=3,556 (%) | Obs=3,489 (%) |
| =<1.5x ULN | 59 (1.66) | 117 (3.35) |
| >1.5x ULN | 8 (0.22) | 6 (0.17) |
| >2x ULN | 6 (0.17) | 6 (0.17) |
| >3x ULN | 6 (0.17) | 3 (0.09) |
| >5x ULN | 3 (0.08) | 0 (0.00) |
| >8x ULN | 1 (0.03) | 0 (0.00) |

*For subjects who received at least one dose of study medication (in safety population), includes all study data since the date of the first double-blind study medication administration;
Obs=Number of non-missing laboratory values; N=number of subjects in safety population
Note: Numbers in parenthesis in the 2nd/3rd columns are percentages of number of subjects over Obs.
Note: Einstein Extension was ongoing at the time of data submission

For the pooled Einstein DVT and PE studies, there were a total of 6 (0.17%) and 6 (0.17%) subjects in the rivaroxaban and enoxaparin arms, respectively, that met the criteria for Hy's Law cases. There were no subjects in the Einstein Extension study that met the criteria for Hy's Law cases. *However, please note that the Einstein PE extension study was ongoing at the time of data submission.*

In order to assess the sensitivity of the ALT and TBL cut-off criteria for Hy's Law cases, the reviewer performed additional analyses by calculating the proportion of cases based on modified

(sensitivity) criteria (1) ALT>2.9x ULN and TBL>1.9x ULN and (2) ALT>2.5x ULN and TBL>1.5x ULN using the pooled data from the Rocket and J-Rocket studies. These analyses resulted in 34 and 40 subjects in the rivaroxaban and warfarin arms, respectively, for criteria (1) and 55 and 56 subjects in the rivaroxaban and warfarin arms, respectively, for criteria (2). Thus, the result using sensitivity criteria (1) revealed an additional 4 subjects in the warfarin arm and 0 (zero) in the rivaroxaban arm using the slightly modified, more conservative, cut-off levels. Similarly, when considering criteria (2), the sensitivity analyses identified additional 21 and 20 cases in the rivaroxaban and warfarin groups, respectively. However, note that the criteria (2) used lower, more conservative, cut-off values and therefore may be viewed less clinically relevant.

**Table 15: ALT>3x ULN Occurrence by Study Window**

| | Rocket, J-Rocket | | Einstein DVT, PE | | Einstein Extension | |
|---|---|---|---|---|---|---|
| **Window** | **Rivaroxaban** | **Warfarin** | **Rivaroxaban** | **Enoxaparin** | **Rivaroxaban** | **Placebo** |
| 0 - <2 wks | 20 (9) | 20 (9) | 20 (34) | **85 (77)** | 0 (0) | 0 (0) |
| 2 wk – 0.5 yr | 86 (40) | 85 (39) | 32 (55) | 22 (20) | 11 (100) | 3 (100) |
| 0.5 yr - <1.0 yr | 65 (30) | 71 (33) | 6 (10) | 4 (4) | | |
| 1.0 yr - <1.5 yr | 24 (11) | 16 (7) | - | - | - | - |
| 1.5 yr - <2.0 yr | 18 (8) | 16 (7) | - | - | - | - |
| 2.0 yr - <2.5 yr | 3 (1) | 9 (4) | - | - | - | - |
| 2.5 yr- <3 yr | 1 (0) | 0 (0) | - | - | - | - |
| **Total** | **217** | **217** | **58** | **111** | **11** | **3** |

Note: Window in Weeks; Numbers in parenthesis are percentages based on column totals on last row
Note: There were no observations after 3 yrs

Occurrences of ALT>3x ULN, TBL>2x ULN by selected pre-specified study time windows are summarized in Tables 15 and 16. The tables show that for the pooled Rocket and J-Rocket studies, the proportion of ALT>3x ULN and TBL>2x ULN were similar between groups per study window. However, in the Einstein DVT and PE studies, a larger proportion of subjects (77%) had ALT>3x ULN from baseline up to week 2 in the enoxaparin arm; after week 2, there were more subjects in the rivaroxaban arm (65%) than in the enoxaparin arm (24%) with ALT>3x ULN.

**Table 16: TBL>2x ULN Occurrence by Study Window**

| | Rocket, J-Rocket | | Einstein DVT, PE | | Einstein Extension | |
|---|---|---|---|---|---|---|
| **Window** | **Rivaroxaban** | **Warfarin** | **Rivaroxaban** | **Enoxaparin** | **Rivaroxaban** | **Placebo** |
| 0 - <2 wks | 29 (18) | 23 (11) | 5 (19) | 3 (14) | 0 | 2 (40) |
| 2 wk – 0.5 yr | 59 (38) | 84 (42) | 20 (74) | 18 (82) | 2 (100) | 3 (60) |
| 0.5 yr - <1.0 yr | 31 (20) | 55 (27) | 2 (7) | 1 (5) | - | - |
| 1.0 yr - <1.5 yr | 19 (12) | 18 (9) | - | - | - | - |
| 1.5 yr - <2.0 yr | 8 (5) | 10 (5) | - | - | - | - |
| 2.0 yr - <2.5 yr | 10 (6) | 7 (3) | - | - | - | - |
| 2.5 yr- <3 yr | 1 (1) | 4 (2) | - | - | - | - |
| **Total** | **157** | **201** | **27** | **22** | **2** | **5** |

Note: Window in Weeks; Numbers in parenthesis are percentages based on column totals on last row
Note: There were no observations after 3 yrs

Hy's Law cases by time window are presented in Table 17 showing that within 1 year more cases occurred in the warfarin arm compared to rivaroxaban. After 1 year, more cases were reported in the rivaroxaban arm compared to warfarin. Specifically, there were only 22% Hy's

Law cases in the warfarin arm that occurred after 1 year and most of the occurrences were prior to 1 year (78%). Hy's Law cases in the rivaroxaban arm seemed to occur uniformly over the first 2.5 years post-randomization; however the number of events is small.

**Table 17: ALT>3x, TBL>2x ULN (Hy's Law Cases) Occurrence by Study Window**

| | Rocket, J-Rocket | | Einstein DVT, PE | |
|---|---|---|---|---|
| **Window** | **Rivaroxaban** | **Warfarin** | **Rivaroxaban** | **Enoxaparin** |
| 0 - <2 wks | 1 (3) | 0 (0) | 2 (33) | 0 |
| 2 wk – 0.5 yr | 9 (26) | 10 (28) | 4 (67) | 5 (83) |
| 0.5 yr - <1.0 yr | 6 (18) | 18 (50) | 0 | 1 (17) |
| 1.0 yr - <1.5 yr | 8 (24) | 2 (6) | - | - |
| 1.5 yr - <2.0 yr | 8 (24) | 5 (14) | - | - |
| 2.0 yr - <2.5 yr | 2 (6) | 1 (3) | - | - |
| **Total** | **34** | **36** | **6** | **6** |

Note: Window in Weeks; Numbers in parenthesis are percentages based on column totals on last row
Note: There were no observations after 2.5 yrs

## (b) Hepatic Disorders Adverse Events

In the pooled Rocket and J-Rocket studies, the proportion of subjects with post-baseline hepatic adverse events (SMQ) was statistically significantly lower [OR=0.68, 95% CI (0.60, 0.76)] in the rivaroxaban arm (526 or 6.8%) compared to the warfarin arm (752 or 9.7%) *[Note: The total numbers of hepatic adverse events, including adverse events in the SMQ, were 645 and 877 in the rivaroxaban and warfarin arms, respectively]*. This difference was primarily driven by a statistically significantly lower [OR=0.25, 95% CI (0.20, 0.32)] proportion of subjects with increased INR in the rivaroxaban arm (90 or 1.2%) compared to the warfarin arm (346 or 4.5%) (Table 18). Among all subjects with increased INR, 19 and 15 cases in the rivaroxaban and warfarin arms, respectively, were reported as serious (see Appendix I A). In addition, the mean (std)/median time (days) to increased INR from first dose was 251 (251)/169 and 561 (247)/577, in the warfarin and rivaroxaban arms respectively.

Analyses of INR by study found a statistically significant difference between treatment arms in the Rocket study (consistent with the pooled analysis). In the J-Rocket study, the direction of the imbalance was reversed, though the difference between arms was not statistically significant. *Note that for the J-Rocket study, there were 0 (zero) treatment emergent increased INR in the Rivaroxaban arm. Hence, for the J-Rocket study, all increased INR events in the Rivaroxaban arm occurred after 2 days past the last dose dates for all subjects.*

Other adverse events (according to PTs in the Hepatic disorders SMQ) for which there was a statistically significant difference detected between treatment groups are also shown in Table 18. There was a statistically significantly higher incidence of reported increased ALT in the rivaroxaban versus the warfarin arm in the Rocket study only. In addition, a statistically significantly lower incidence of reported increased AST in the rivaroxaban versus the warfarin arm in the J-Rocket study only was found. There was a statistically significantly higher incidence of reported cholelithiasis in the rivaroxaban versus the warfarin arm in both the pooled, and Rocket only analyses. *A full list of PTs in the Hepatic disorders SMQ and the Hepatobiliary disorders SOC for adverse events that occurred after the first dose of drug administration in the pooled Rocket and J-Rocket studies is provided in Appendix I A.*

**Table 18: Post-baseline Hepatic-Related AEs in Rocket and J-Rocket Studies***

| MedDRA PT | Rivaroxaban | Warfarin | Odds Ratio** (95% CI) |
|---|---|---|---|
| **Alanine aminotransferase increased** | | | |
| Rocket | 147/7,111 (2.1) | 113/7,125 (1.6) | **1.31 (1.02,1.68)** |
| J-Rocket | 20/639 (3.1) | 21/639 (3.3) | 0.95 (0.51,1.77) |
| Pooled | 167/7,750 (2.2) | 134/7,764 (1.7) | 1.25 (1.00,1.58) |
| **Aspartate aminotransferase increased** | | | |
| Rocket | 28/7,111 (0.4) | 27/7,125 (0.4) | 1.04 (0.61,1.77) |
| J-Rocket | 5/639 (0.8) | 17/639 (2.7) | **0.29 (0.10,0.79)** |
| Pooled | 33/7,750 (0.4) | 44/7,764 (0.6) | 0.75 (0.48,1.18) |
| **Cholelithiasis** | | | |
| Rocket | 76/7,111 (1.1) | 47/7,125 (0.7) | **1.63 (1.13,2.34)** |
| J-Rocket | 7/639 (1.1) | 6/639 (0.9) | 1.16 (0.39,3.50) |
| Pooled | 83/7,750 (1.1) | 53/7,764 (0.7) | **1.57 (1.11,2.22)** |
| **INR increased** | | | |
| Rocket | 63/7,111 (0.9) | 329/7,125 (4.6) | **0.18 (0.14,0.24)** |
| J-Rocket | 27/639 (4.2) | 17/639 (2.7) | 1.61 (0.87,3.00) |
| Pooled | 90/7,750 (1.2) | 346/7,764 (4.5) | **0.25 (0.20,0.32)** |

* Analyses based on incidence of subjects with events and not of events overall, based on SMQ queries
**Odds ratio (unadjusted) comparing rivaroxaban versus warfarin
Note: Pooled=Rocket and J-Rocket

Analyses of total number of events were also performed on the (1) Hepatic disorders SMQ excluding (i) Liver related coagulation and bleeding disturbances subsearch SMQ (i) Liver related coagulation and bleeding disturbances subsearch SMQ and the Liver related investigations, signs and symptoms subsearch SMQs and the (2) Hepatobiliary disorders system organ class (SOC). These analyses considered all post-baseline AEs, treatment emergent AEs, AEs that occurred within 30 days from the last dose date, serious AEs and AEs leading to permanent study drug discontinuation. The results of these analyses did not identify any statistically significant differences between the rivaroxaban and warfarin pooled treatment groups.

*Note: The Liver related coagulation and bleeding disturbances and the Liver related investigations, signs and symptoms SMQs were also considered separately in the analyses. There were no statistically significant differences between treatment arms observed for total AE incidences in these SMQs and for individual PTs in these SMQs.*

Table 19 summarizes the hepatic adverse events in which there were numerical differences between treatment arms among the 70 Hy's Law cases identified in the Rocket and J-Rocket studies. The purpose of this additional analysis is to summarize hepatic-related events among Hy's Law cases and not to provide any statistical comparisons.

***Reviewer's Comment: This analysis is limited by the fact that liver function tests abnormal preferred terms data were provided for only 18 (8 rivaroxaban/10 warfarin)/70 Hy's Law cases.***

Table 19: Hepatic adverse events among identified Hy's Law Cases

| Adverse Events among the Hy's Law cases* | Rivaroxaban (n=34) | Warfarin (n=36) |
|---|---|---|
| Alanine aminotransferase (ALT) increased | 7 | 0 |
| Aspartate aminotransferase (AST) increased | 4 | 0 |
| Cholelithiasis | 7 | 2 |

*Data available only for 8 and 10 of the 34 rivaroxaban and 36 warfarin cases, respectively.

Table 20 shows that the incidences of increased ALT, increased INR, and abnormal liver function tests (based on reported PTs) were lower in the rivaroxaban arm compared to enoxaparin in the pooled and individual study analyses of the Einstein only studies. Most of the estimated unadjusted odds ratios and 95% confidence intervals exclude one favoring rivaroxaban. No differences were noted in the incidence of cholelithiasis or of increased AST between treatment groups in the pooled and individual study analyses (results not presented).

**Table 20: Summary of Post-baseline Adverse Events in Einstein DVT and PE Studies***

| MedDRA PT | Rivaroxaban | Enoxaparin | Odds Ratio** (95% CI) |
|---|---|---|---|
| **ALT increased** | | | |
| Pooled | 60/3,729 (1.6) | 111/3,703 (3.0) | **0.53 (0.39,0.73)** |
| Einstein DVT | 24/1,718 (1.4) | 55/1,711 (3.2) | **0.43 (0.26,0.69)** |
| Einstein PE | 36/2,011 (1.8) | 56/1,992 (2.8) | **0.63 (0.41,0.96)** |
| **INR increased** | | | |
| Pooled | 9/3,729 (0.2) | 87/3,703 (2.4) | **0.10 (0.05,0.20)** |
| Einstein DVT | 2/1,718 (0.1) | 41/1,711 (2.4) | **0.05 (0.01,0.20)** |
| Einstein PE | 7/2,011 (0.4) | 46/1,992 (2.3) | **0.15 (0.07,0.33)** |
| **Liver function tests abnormal** | | | |
| Pooled | 25/3,729 (0.7) | 47/3,703 (1.3) | **0.53 (0.32,0.85)** |
| Einstein DVT | 9/1,718 (0.52) | 21/1,711 (1.2) | **0.42 (0.19,0.93)** |
| Einstein PE | 16/2,011 (0.8) | 26/1,992 (1.3) | 0.61 (0.32,1.13) |

* Analyses based on incidence on number of subjects and not on the number of events
**Odds ratio (unadjusted) comparing rivaroxaban versus warfarin
Note: Pooled Einstein DVT and PE studies

In the Einstein Extension study, there were 4 cases of reported increased hepatic enzyme and 3 cases of cholelithiasis in the rivaroxaban arm compared to no cases in the placebo arm. No other events were noted as occurring more frequently in the rivaroxaban arm vs. placebo.

*Lists of PTs in the Hepatobiliary disorders SOC for adverse events that occurred after the first dose of drug administration in the pooled Einstein DVT and PE studies, and the Einstein Extension study are provided in Appendix I B and C.*

*Note: The Hepatobiliary disorders SOC included 123 and 119 events in the pooled rivaroxaban and enoxaparin arms, respectively, of which none of the events were statistically different between the treatment arms. The adverse events reported in Table 20 were not in the Hepatobiliary disorders SOC.*

# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses by gender, race and age were performed for the Rocket study only since the majority of data originated from this study.

**ALT>3x ULN**

There were 228 (~3%) and 243 (~3%) rivaroxaban and warfarin subjects, respectively, with ALT>3x ULN elevations. There were proportionally more male subjects in the warfarin arm compared to male subjects in the rivaroxaban arm with elevated ALT as shown in Table 21. With respect to reported race, there were 15 more cases of elevated ALT among Asian subjects in the warfarin arm compared to rivaroxaban. No differences were statistically significant and therefore do not suggest an interaction between gender, race and treatment. There were no notable differences between treatment arms within age and country subgroups.

**Table 21: Analysis of ALT>3x ULN by Gender and Race in the Rocket Study**

| Subgroup | Rivaroxaban N=228 (%) | Warfarin N=243 (%) | Total N=471 (%) |
|---|---|---|---|
| **Gender** | | | |
| Female | 111 (49) | 101 (42) | 212 (45) |
| Male | 117 (51) | **142 (58)** | 259 (55) |
| **Race** | | | |
| American Indian or Alaskan Native | 0 (0) | 1 (0) | 1 (0) |
| Asian | 31 (14) | **46 (19)** | 77 (16) |
| Black or African American | 3 (1) | 2 (1) | 5 (1) |
| Native Hawaiian or Other Pacific Islander | 0 (0) | 1 (0) | 1 (0) |
| Other | 8 (3) | 4 (2) | 12 (3) |
| White | 186 (82) | 189 (78) | 375 (80) |

**TBL>2x ULN**

There were 191 (~3%) and 236 (~3%) rivaroxaban and warfarin subjects, respectively, with TBL>2x ULN elevations (results not shown). The gender [male (78%) and female (22%)] as well as race [White (78%) and Asian (18%)] proportions of TBL elevations were similar in each arm. There were no notable patterns or differences between treatment arms for the age and country subgroups.

**Hy's Law Cases (ALT>3x ULN and TBL>2x ULN)**

There were 31 (<1%) and 33 (<1%) rivaroxaban and warfarin subjects, respectively, that met the Hy's Law criteria of ALT>3x ULN and TBL>2x ULN in the Rocket study. Subgroup counts are provided in Table 22. There were no distinguishable patterns or differences between treatment arms in any of the subgroups.

**Table 22: Subgroups for Hy's Law Cases in the Rocket Study**

| Subgroup | Rivaroxaban N=31 (%) | Warfarin N=33 (%) | Total N=64 |
|---|---|---|---|
| **Age (Years)** | | | |
| <50 | 2 (6) | 2 (6) | 4 (6) |
| 50 - <60 | 4 (13) | 2 (6) | 6 (9) |
| 60 - <70 | 8 (26) | 10 (30) | 18 (28) |
| 70 - <80 | 13 (42) | 12 (36) | 25 (39) |
| >80 | 4 (13) | 7 (21) | 11 (17) |
| **Gender** | | | |
| Female | 10 (32) | 13 (39) | 23 (36) |
| Male | 21 (68) | 20 (61) | 41 (64) |
| **Race** | | | |
| American Indian or Alaskan Native | 0 (0) | 1 (3) | 1 (2) |
| Asian | 5 (16) | 8 (24) | 13 (20) |
| Black or African American | 0 (0) | 1 (3) | 1 (2) |
| Native Hawaiian or Other Pacific Islander | 0 (0) | 0 (0) | 0 (0) |
| Other | 0 (0) | 1 (0) | 1 (2) |
| White | 26 (84) | 22 (67) | 48 (74) |

# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

Most of the laboratory values for ALT and TBL in the Rocket and J-Rocket studies were available only up to one year after treatment initiation. That is, approximately 80% of subjects from baseline had hepatic laboratory assessments by one year and only 44% in two years. The large amount of missing values after the one-year follow-up visit is a major factor that should be considered when interpreting the results after one-year. It is possible that the amount of missing data might contribute to a less precise estimate for the laboratory parameters presented in this review. Note that the expected study duration for the Rocket study was 32 months (<3 years) and subjects could be followed up to a maximum of 4 years. The numbers of missing ALT and TBL data beyond one year were about the same in each treatment arm. The medication completion rates in the Rocket and J-Rocket studies were 65% and 75%, respectively, and early study medication discontinuation were due mainly to adverse events or withdrawal of consent.

Other issues and data limitations include the following:

- **Low Statistical Power to Detect Event Rates**: The event rates for ALT>5x and higher thresholds, and TBL>3x and higher thresholds were low. Calculated hazard ratios using the Cox model may not have sufficient power to detect any differences between the treatment arms.
- **Varying MedDRA coding versions**: Adverse events in the Rocket, Einstein DVT and Einstein PE studies were coded using MedDRA 13.0 while those in the J-Rocket and Einstein Extension studies were coded using MedDRA 12.1 and MedDRA 12.0, respectively. Results from the pooling of adverse events across the Rocket and J-Rocket studies may not be accurate since PT terms of interest varied by version. The overall impact is minimal given that the Rocket study is much larger than the J-Rocket study thus contributing the majority of information.
- **Conversion of Original to Standardized Laboratory Values:** The original laboratory units of measure, which often differed across centers and regions, were standardized. There were also some original values that were reported with inequality signs (< or >) or that may have been incorrectly coded using "," instead of "." These conversions were documented by the applicant and did not appear to impact the overall hepatic safety analysis.
- **Central and Local Laboratory Values**: Some analyses were performed based on central laboratory values alone while others used both central and local values. No major differences were noted in analyses that considered values from both laboratories compared to those from one laboratory. However, given the small event rates, differences might not be apparent.
- **Dataset Variable for Treatment Assignment**: The variable "TRTP" (for "Planned Treatment") was the only available variable in the datasets reviewed that distinguishes treatment groups and was used by the reviewer in all analyses in this report. However, TRTP represents *actual* treatment for the Einstein DVT, PE and Extension studies, and *planned treatment* for Rocket and J-Rocket studies. The actual treatment assignments in the Rocket studies may be different from the planned treatment and hence, the analyses results might also be different.

The proportions of subject with elevations of ALT>3x ULN were generally balanced between treatment arms in the Rocket studies, lower in the rivaroxaban arm compared to the enoxaparin arm in the Einstein DVT/PE studies, and higher in the rivaroxaban arm compared to placebo in the Einstein Extension study. The noted imbalances in the Einstein studies mostly occurred due to differences between groups for ALT >3x ULN and ALT>5x ULN thresholds.

The analysis of total bilirubin suggests that the proportions of subjects with elevations of >1.5x ULN or >2x ULN were lower in the rivaroxaban arm compared to warfarin in the pooled Rocket studies and higher in the rivaroxaban arm compared to enoxaparin in the pooled Einstein studies (mainly for >1.5x ULN).

Analyses by study time windows showed that the occurrences of ALT>3x ULN and TBL>2x ULN were roughly similar per treatment arm in the Rocket and J-Rocket studies. However, in the Einstein DVT and PE studies there was a large proportion of subjects (77%) who had

ALT>3x ULN from baseline up to week 2 in the enoxaparin arm; after week 2, there were more subjects in the rivaroxaban arm (65%) than in the enoxaparin arm (24%) with ALT>3x ULN.

There were 34 and 36 subjects in the rivaroxaban and warfarin arms, respectively, that met the criteria of Hy's Law cases (ALT>3x ULN and TBL>2x ULN) in the pooled Rocket studies and 6 in each arm in the pooled Einstein DVT/PE studies (none were reported in the Einstein Extension study). The average time (standard deviation) from first dose administration until the occurrence of Hy's Law cases (among Hy's Law cases only) in the Rocket studies was longer in the rivaroxaban arm [412 (260) days] compared to the warfarin arm [329 (206) days]. By summarizing the occurrences of Hy's Law cases by study time windows, the cases in the rivaroxaban arm appeared to occur uniformly over 2.5 years post randomization while most occurrences in the warfarin arm were within the first year (78%). In a time-to-event analysis that includes censored observations (i.e. no events at end of study), the estimated hazard ratio (95% CI) was 0.95 (0.60, 1.52). Sensitivity analyses using lower, more conservative, cut-offs for ALT and TBL, revealed that there were no major imbalances in the number of Hy's Law cases between the rivaroxaban arm and active-control. As previously reported, there were 10 Hy's Law cases identified in both treatment arms in the pooled RECORD trials (the rivaroxabin dose was 10 mg/daily consistent with the proposed dose for indication being sought) in all four RECORD trials and the enoxaparin dose was 40 mg daily in RECORD 1, 2, and 3 and 30 mg twice daily in RECORD 4).

There were specific adverse events (reported as MedDRA PTs) that were not balanced between the rivaroxaban and active control treatment arms. In the pooled Rocket studies, there were generally more patients with increased ALT and reported cholelithiasis in the rivaroxaban arm compared to warfarin. Conversely, the proportion of patients with reported increased AST or increased INR was lower in the rivaroxaban arm compared to the warfarin arm in the pooled Rocket studies. Similarly, the mean onset time for increased INR was shorter in the warfarin compared to rivaroxaban in the pooled Rocket studies.

In the pooled Einstein studies, the proportions of patients with increased INR and increased ALT were lower in the rivaroxaban arm compared to enoxaparin.

### 5.2 Conclusions and Recommendations

The overall interpretation of findings from this statistical safety review should consider the various differences in study design across the five studies. Although all five studies assessed long-term doses of rivaroxaban, the treatment duration assessed in the Rocket studies was longer (2-4 years) compared to the duration in the Einstein studies (up to 1 year). Note that although subjects were followed up to a maximum of 4 years in the Rocket study, most hepatic laboratory measurements were available only up to 1 year with a decline in measurements by 2 years follow-up (approximately 44% of subjects from baseline). In addition, the active-control treatments differed; warfarin was used in the Rocket studies whereas enoxaparin was the control used in the Einstein studies (except for Einstein Extension which was placebo-controlled). Further, the Rocket studies were double-blind in design compared to the Einstein studies, which were open-label (except for Einstein Extension which was also double-blind). In addition, these five trials studied larger rivaroxaban doses given for longer durations compared to intended dose

of 10 mg/daily for either 35 or 14 days for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. Results from these analyses provide additional information to that summarized previously for the RECORD 1-4 studies, regarding the safety of rivaroxaban when given at lower doses and for shorter durations.

Results from liver function tests suggest that rivaroxaban is comparable to warfarin or enoxaparin in terms of elevations of ALT>3x ULN, TBL>2x ULN, or joint ALT>3x ULN and TBL>2x ULN (Hy's Law cases). However, comparisons for higher elevation cut-offs were difficult to assess because of the low power in the Cox model to detect differences based on low incidence rates in each treatment arm. Although the number of Hy's Law cases in each arm were comparable in the Rocket studies (warfarin comparator) and the incidences were low (0.5% per arm), the timing of the cases were largely uniform over 2.5 years in the rivaroxaban arm while most cases in the warfarin arm occurred within the first year. Analyses of reported adverse events showed that there are significant imbalances between treatment arms for increased ALT (in favor of warfarin in the Rocket study and in favor of rivaroxaban in the Einstein DVT/PE studies), cholelithiasis (in favor of warfarin), increased AST (in favor of rivaroxaban in the J-Rocket studies), and increased INR (in favor of rivaroxaban in the Rocket and Einstein DVT/PE studies). For increased INR, the treatment differences suggested fewer events in the rivaroxaban arm versus active control trials, except for the J-Rocket trial, and onset was mostly later in the rivaroxaban arm compared to the warfarin arm.

In conclusion, this review did not identify any significant increases in specific liver parameters of interest including ALT, TBL, incidence of Hy's Law cases, and specific hepatic adverse events among patients treated with rivaroxaban (at doses ranging from 10-30 mg for up to four years) compared to patients receiving either warfarin, enoxaparin, or placebo across five randomized clinical trials. Findings indentified similar proportion of Hy's Law cases in the pooled Rocket trials between treatment arms; however the time to event was shorter in the warfarin control versus rivaroxaban.

## APPENDIX I: Hepatic Adverse Events by MedDRA Preferred Term
## A. Rocket and J-Rocket

| Group by Treatment | | Planned Treatment | |
|---|---|---|---|
| | | Rivaroxaban | Warfarin |
| | | N | N |
| **Group** | **Dictionary-Derived Term** | | |
| **Hepatic disorders SMQ** | **Alanine aminotransferase increased** | **167 (5)** | **134 (0)** |
| | Ascites | 9 (2) | 11 (4) |
| | **Aspartate aminotransferase increased** | **33 (3)** | **44 (1)** |
| | Benign hepatic neoplasm | . | 1 |
| | Bilirubin conjugated increased | 6 (1) | 10 (0) |
| | Blood alkaline phosphatase increased | 17 (1) | 10 (0) |
| | Blood bilirubin increased | 46 (3) | 63 (0) |
| | Blood bilirubin unconjugated increased | . | 1 |
| | Cytomegalovirus hepatitis | 1 | . |
| | Gamma-glutamyltransferase increased | 8 | 12 |
| | Gastric varices | . | 1 (1) |
| | Gastric varices haemorrhage | 1 (1) | . |
| | Haemangioma of liver | 2 | 1 |
| | Hepatic adenoma | . | 1 (1) |
| | Hepatic cancer metastatic | 1 (1) | 2 (2) |
| | Hepatic encephalopathy | 1 (1) | . |
| | Hepatic enzyme abnormal | . | 2 (2) |
| | Hepatic enzyme increased | 31 (8) | 36 (12) |
| | Hepatic neoplasm | . | 3 (1) |
| | Hepatic neoplasm malignant | 2 (2) | 2 (2) |
| | Hepatitis B | 2 (1) | 5 (2) |
| | Hepatitis B surface antigen positive | 1 | . |
| | Hepatitis C | 4 (3) | 6 (5) |
| | Hepatitis C antibody positive | . | 1 |
| | Hepatitis E | 3 (1) | . |
| | Hepatitis E antibody positive | 1 | . |
| | Hepatitis viral | . | 1 (1) |
| | Hypoalbuminaemia | 1 | 1 |
| | International normalised ratio abnormal | 1 | 5 (2) |
| | **International normalised ratio increased** | **90 (19)** | **346 (15)** |
| | Liver abscess | 2 (2) | . |
| | Liver function test abnormal | 47 (10) | 34 (14) |
| | Liver scan abnormal | 1 | . |

| Group by Treatment | | Planned Treatment | |
|---|---|---|---|
| | | Rivaroxaban | Warfarin |
| | | N | N |
| | Oesophageal varices haemorrhage | 1 (1) | 1 (1) |
| | Portal hypertensive gastropathy | 1 | . |
| | Prothrombin level decreased | . | 1 (1) |
| | Prothrombin time prolonged | 2 (1) | 1 |
| | Transaminases increased | 7 (1) | 4 (2) |
| | Urobilin urine present | 1 | 2 |
| | Varices oesophageal | 6 (1) | 4 (1) |
| | X-ray hepatobiliary abnormal | 1 | . |
| | **All** | **497 (68)** | **746 (70)** |

| Group by Treatment | | Planned Treatment | |
|---|---|---|---|
| | | Rivaroxaban | Warfarin |
| | | N | N |
| **Hepatobiliary disorders SOC** | **Dictionary-Derived Term** | | |
| | Acute hepatic failure | . | 1 (1) |
| | Alcoholic liver disease | 4 | . |
| | Bile duct obstruction | 2 (2) | 1 (1) |
| | Bile duct stone | 6 (4) | 9 (9) |
| | Biliary colic | 6 (2) | 4 (2) |
| | Biliary dilatation | 1 | 2 |
| | Biliary dyskinesia | . | 2 |
| | Biliary tract disorder | 1 | . |
| | Cardiac cirrhosis | 3 (2) | 2 (1) |
| | Cholangitis | 8 (7) | 3 (2) |
| | Cholangitis acute | 2 (2) | . |
| | Cholangitis sclerosing | . | 1 (1) |
| | Cholecystitis | 14 (7) | 18 (14) |
| | Cholecystitis acute | 31 (22) | 26 (17) |
| | Cholecystitis chronic | 10 (6) | 4 (0) |
| | **Cholelithiasis** | **83 (20)** | **53 (16)** |
| | Cholelithiasis obstructive | . | 1 (1) |
| | Cholestasis | 2 (0) | 2 (1) |
| | Chronic hepatitis | 1 | . |
| | Cryptogenic cirrhosis | . | 2 (2) |
| | Cytolytic hepatitis | 4 (2) | 4 (0) |
| | Fatty liver alcoholic | 1 | . |
| | Gallbladder disorder | 2 | . |
| | Gallbladder fistula | 1 (1) | . |
| | Gallbladder pain | 2 | . |
| | Gallbladder polyp | 4 | 1 |
| | Haemobilia | 1 | . |
| | Haemorrhagic hepatic cyst | . | 1 (1) |
| | Hepatic cirrhosis | 6 (3) | 6 (2) |
| | Hepatic congestion | 4 (1) | 2 (0) |
| | Hepatic cyst | 15 | 12 |
| | Hepatic failure | . | 1 (1) |
| | Hepatic fibrosis | . | 1 |

| Group by Treatment | Planned Treatment | |
|---|---|---|
| | Rivaroxaban | Warfarin |
| | N | N |
| Hepatic function abnormal | 24 (1) | 23 (1) |
| Hepatic haemorrhage | 1 (1) | . |
| Hepatic lesion | 4 | 1 |
| Hepatic mass | 1 | 1 |
| Hepatic pain | 2 | 2 |
| Hepatic steatosis | 37 (2) | 33 (2) |
| Hepatic vein dilatation | . | 1 |
| Hepatitis | 3 (1) | 1 (1) |
| Hepatitis acute | 1 (1) | 1 (1) |
| Hepatitis alcoholic | 2 | . |
| Hepatitis cholestatic | 1 | . |
| Hepatitis chronic active | 1 | . |
| Hepatomegaly | 7 | 6 |
| Hyperbilirubinaemia | 16 | 12 |
| Hyperplastic cholecystopathy | 1 | . |
| Hypertransaminasaemia | . | 1 |
| Ischaemic hepatitis | 1 (1) | 3 (3) |
| Jaundice | 3 (0) | 3 (2) |
| Jaundice cholestatic | 2 (1) | 2 (2) |
| Jaundice hepatocellular | . | 1 (1) |
| Liver disorder | 6 (2) | 9 (0) |
| Portal vein thrombosis | 1 (1) | . |
| **All** | **328 (92)** | **259 (85)** |

Note: These are adverse events that occurred post-baseline. Numbers in parenthesis are serious PTs

## B. Einstein DVT/PE

| Hepatobiliary SOC | Planned Treatment | |
|---|---|---|
| | Enoxaparin | Rivaroxaban |
| | N | N |
| **MEDDRA PREFERRED TERM** | | |
| Acute hepatic failure | 1 (1) | . |
| Bile duct stenosis | . | 1 |
| Bile duct stone | . | 1 (1) |

| Hepatobiliary SOC | Planned Treatment | |
|---|---|---|
| | Enoxaparin | Rivaroxaban |
| | N | N |
| Biliary cirrhosis primary | 1 | . |
| Biliary colic | 2 (1) | 2 (1) |
| Cholangitis | 3 (1) | 3 (2) |
| Cholangitis sclerosing | . | 1 |
| Cholecystitis | 5 (3) | 2 (1) |
| Cholecystitis acute | 4 (3) | . |
| Cholecystitis chronic | 1 | 2 |
| Cholelithiasis | 24 (4) | 23 (5) |
| Cholestasis | . | 2 |
| Cytolytic hepatitis | . | 1 (1) |
| Gallbladder polyp | 1 | 4 |
| Hepatic cirrhosis | 2 | 1 |
| Hepatic congestion | . | 1 |
| Hepatic cyst | 11 | 11 |
| Hepatic failure | 3 (3) | 1 (1) |
| Hepatic function abnormal | 11 (1) | 8 (0) |
| Hepatic mass | 2 (0) | 1 (1) |
| Hepatic pain | . | 1 (1) |
| Hepatic steatosis | 31 (1) | 42 (0) |
| Hepatitis | 1 (1) | 1 (0) |
| Hepatitis acute | . | 2 (2) |
| Hepatitis chronic active | . | 1 (1) |
| Hepatocellular injury | 1 | . |
| Hepatomegaly | 5 | 7 |
| Hydrocholecystis | 1 | . |
| Hyperbilirubinaemia | 1 | 1 |
| Hypertransaminasaemia | 2 | . |
| Ischaemic hepatitis | . | 1 (1) |
| Jaundice | 1 | 1 (1) |
| Jaundice cholestatic | 1 (1) | . |
| Liver disorder | 2 | . |
| Liver injury | 1 | 1 |
| Portal hypertension | 1 | . |
| All | **119 (20)** | **123 (19)** |

| Hepatobiliary SOC | Planned Treatment | |
|---|---|---|
| | Enoxaparin | Rivaroxaban |
| | N | N |

Note: These are adverse events that occurred post-baseline. Numbers in parenthesis are serious PTs

## C. Einstein Extension

| Hepatobiliary SOC | Planned Treatment | |
|---|---|---|
| | Placebo | Rivaroxaban |
| | N | N |
| **MEDDRA PREFERRED TERM** | | |
| Biliary colic | 2 | . |
| Cholecystitis | 1 (1) | 1 (1) |
| Cholelithiasis | . | 3 (1) |
| Cholestasis | 1 | . |
| Hepatic steatosis | . | 2 |
| All | **4 (1)** | **6 (2)** |

Note: These are adverse events that occurred post-baseline. Numbers in parenthesis are serious PTs

## SIGNATURES/DISTRIBUTION LIST

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/s/

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06/10/2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## ADDENDUM

| | |
|---|---|
| **NDA/BLA Serial Number:** | 22-406/0059 |
| **Drug Name:** | Rivaroxaban (Xarelto) |
| **Indication(s):** | For the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery |
| **Applicant:** | Johnson & Johnson Pharmaceutical Research & Development |
| **Date(s):** | Date submitted: 1/03/2011 |
| | PDUF Date : 7/03/2011 |
| **Review Priority:** | Priory review |
| **Biometrics Division:** | Division of Biometrics V (HFD-711) |
| **Statistical Reviewer:** | Qing Xu, Ph.D |
| **Concurring Reviewers:** | Mark Rothmann, Ph.D |
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| **Clinical Team:** | Min Lu, MD |
| | Kathy Rubie Sue, M.D., Ph.D. |
| | Ann T Farrell, M.D |
| **Project Manager:** | Tyree Newman |

# 1. EXECUTIVE SUMMARY

This addendum is to provide statistical review comments on the sponsor's resubmission NDA 022406/0059 dated January 03, 2011. Reference is made to the statistical report to the original NDA 22-406 signed on May 08, 2009. The sponsor's resubmission is the responses to the agency's Complete Response (CR) letter dated May 27, 2010. In the CR letter, the FDA identified concerns over the safety findings of a potential risk for serious liver toxicity and findings through the clinical investigator inspection. Thus, this resubmission includes the sponsor's responses to the CR letter.

Primary efficacy analyses results from reviewing original NDA of four multi-center, randomized controlled trials (RECORD 1-4) indicated statistical superiority of rivaroxaban over enoxaparin in the primary efficacy outcome (composite endpoint of any DVT, nonfatal PE, and death from all cause). In this resubmission, the reviewer conducted analysis by excluding all unreliable sites indentified by the Division of Scientific Investigations (DSI); and the results did not alter the original efficacy conclusion. Please refer to the safety statistical report by Dr. John Yap and clinical review report by Dr. Min Lu for the safety conclusions and recommendations for this resubmission.

# 2. BACKGROUD

In this section, we give a brief introduction to clinical study of RECORD 1-4. Please refer to the statistical report signed on May 08, 2009 for the detailed study design and efficacy results for these four multi-center, randomized controlled trials (RECORD 1-4).

The sponsor's original NDA submission for rivaroxaban included four Phase III studies (RECORD 1-4). All four Phase III pivotal studies were similarly designed with identical efficacy and safety parameters measured. They were randomized, double-blinded, double-dummy, active-controlled, multinational studies using rivaroxaban in the treatment of patient with VTE. For four Phase III studies, the primary efficacy endpoint was a composite of incidences of any DVT (proximal and/or distal DVT that were asymptomatic or symptomatic), non-fatal PE, or all cause death (total VTE). The major secondary efficacy endpoints included the incidence of major VTE, incidence of DVT, incidence of symptomatic VTE and net clinical benefit. The efficacy analysis was based on modified intent-to-treat (MITT) population which consisted of subjects who were valid for safety analysis, had undergone the appropriate surgery, and had an adequate assessment of thromboembolism.

RECORD 1 and 2 studies were conducted in patients undergoing hip replacement surgery (THR); RECORD 3 and 4 studies were conducted in patients undergoing knee replacement surgery (TKR). The study indicated statistical superiority of rivaroxaban over enoxaparin in the primary efficacy outcome. The primary efficacy results for total VTE for RECORD (1-4) are provided in table 1 below.

Table 1. Summary of Primary Efficacy Endpoint Analysis Results (Total VTE)

| Study | Rivaroxaban % (n/N) | Enoxaparin % (n/N) | ARR | p-value |
|---|---|---|---|---|
| RECORD 1 | 1.1% (18/1595) | 3.7% (58/1558) | 2.6% | P<0.0001 |
| RECORD 2 | 2.0% (17/864) | 9.3% (81/869) | 7.3% | P<0.0001 |
| RECORD 3 | 9.6% (79/824) | 18.9% (166/878) | 9.3% | P<0.0001 |
| RECORD 4 | 6.9% (67/965) | 10.1% (97/959) | 3.2% | P=0.012 |

ARR=Absolute Risk Reduction

## 3. STATISTICAL EVALUATION

During the review of the clinical studies for this original NDA, DSI became aware of study conduct issues for some investigators and sites. The unreliable sites that were identified by DSI are listed below:

RECORD 1:

- Lenart Site 46002
- Porvaneckas Site 57001
- Slappendel Site 30002

RECORD 2:

- Corces Site 14012
- Yang Site 54005
- Naraffete Site 32005
- Ono Site 50005

RECORD 3:

- Brabants Site 28015

RECORD 4:

- David Loucks Site 14012
- Ricardo Esquivel Site 32006
- R. Michael Murray Site 14005
- John Ward Site 14010
- Craig Buettner Site 14004
- Bharat Mody Site 60010

- Victor Sepulveda Site 32002
- V. Shah Site 60006

The reviewer performed analysis by excluding all these unreliable sites for each of the RECORD study for the primary efficacy endpoint of composite of incidence of any DVT, non-fatal PE, or all cause death (total VTE). The results did not alter the original efficacy conclusion that rivaroxiaban is statistically superior over enoxaparin in the primary efficacy outcome. Table 2 below gave the efficacy results for the total VTE by excluding unreliable sites.

Table 2. Summary of Primary Efficacy Endpoint Analysis Results (Total VTE) Excluding Unreliable Sites

| Study | Rivaroxaban | Enoxaparin | ARR | P-value |
|---|---|---|---|---|
| RECORD 1 | 1.1% (17/1513) | 3.9% (57/1473) | 2.8% | p<0.0001 |
| RECORD 2 | 2.1% (17/828) | 8.4% (70/830) | 6.3% | p<0.0001 |
| RECORD 3 | 9.7% (79/813) | 18.8% (164/871) | 9.1% | p<0.0001 |
| RECORD 4 | 7.1% (53/742) | 10.8% (79/731) | 3.7% | P=0.0174 |

ARR=Absolute Risk Reduction

## 4 CONCLUSION

The review analysis results for the primary efficacy endpoint of total VTE by excluding unreliable sites for each of the RECORD study did not alter the original efficacy conclusion that rivaroxiaban is statistically superior over enoxaparin in the primary efficacy outcome of total VTE in the treatment of patient with VTE

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Date: 5/19/2011

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 22-406/0000 |
| **Drug Name:** | Rivaroxaban (Xarelto) |
| **Indication(s):** | For the prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery |
| **Applicant:** | Johnson & Johnson Phamaceutical Research & Development |
| **Date(s):** | Date submitted: 07/31/2008 |
| | PDUFA due date: 5/14/09 |
| | Review completion date: 5/4/09 |
| **Review Priority:** | Standard review |
| | |
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**Keywords: Venous Thromboembolism, VTE, thrombosis, DVT, Superiority, Non-inferiority, Mantel-Haenszel Analysis Meta Analysis**

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

Four Phase III pivotal clinical studies were included in this New Drug Application (NDA) submission. Statistical analysis results, based on the data of the 4 pivotal studies, demonstrate the drug efficacy using Rivaroxaban in the treatment of major VTE when compared with Enoxaparin control. Findings from using different approaches to deal with missing data issues with the primary endpoint consistently concluded the robustness of the primary efficacy results.

However, the primary efficacy endpoint was the incidence of total VTE that defined as the composite of any DVT, non-fatal PE, or all cause death. Among the 3 components of the composite endpoint, only incidence of DVT in Rivaroxaban group was significantly lower than that in active-control group. In all four pivotal studies, incidences of PE and all cause death were rare. No conclusions can be drawn regarding treatment effect of Rivaroxaban on PE and all cause death, when compared to Enoxaparin control. It is suggested to include this fact in labeling if approval is granted.

All RECORD study protocols included several secondary efficacy endpoints. However, the study statistical analysis plans or SAPs did not include strong control Type I error rate for confirmatory evidence of benefit based on secondary endpoints. A clinically important endpoint in these patient populations is Symptomatic VTE or Death. However Nominal p-values for this secondary endpoints were <0.05 only for RECORD 2 and RECORD 3 studies which used shorter duration of treatment in RECORD 2 and used unapproved lower Enoxaparin regimen in RECORD 3 study. Data from these trials are likely to have resulted in underestimation of Enoxaparin's benefit in terms of Symptomatic VTE. The pooled analysis from this reviewer shows that Rivaroxaban does not have statistically significant difference for Symptomatic VTE compared to Enoxaparin. From the bleeding analysis result, it demonstrated that Rivaroxaban increases the bleeding event compared to Enoxaparin. These issues should be addressed in labeling.

## 1.2 Brief Overview of Clinical Studies

There were four Phase III and four Phase II studies were included in the NDA submission for Agency review. This statistical review report has focused on the four pivotal studies only. All of the four Phase III pivotal studies were designed to be similar and identical in the efficacy and safety parameters measured. They were randomized, double-blinded, double-dummy, active-controlled, multinational studies using Rivaroxaban in the treatment of patient with VTE. The four Phase III pivotal studies are briefly described as following:

**Study 11354 (RECORD 1):** A prospective, randomized, active-comparator controlled, multinational study with a double-blind, parallel-group design to assess the efficacy and safety of 10 mg Rivaroxaban once daily dosing in extended prevention of VTE in man and women aged ≥ 18 years undergoing elective total hip replacement (THR). The planned treatment duration was 35±4 days. A total of 4,541 subjects were randomized to either Rivaroxaban group (n=2,266) or Enoxaparin (n=2,275).

**Study 11355 (RECORD 4):** A prospective, randomized, double-blind, double-dummy, parallel-group, active-comparator controlled, multicenter, multinational study designed to assess the efficacy and safety of Rivaroxaban 10 mg once daily dosing in prevention of VTE in men and women aged 18 years or above undergoing elective total knee replacement (TKR). A total of 2,509 subjects were randomized to either Rivaroxaban group (n=1,252) or Enoxaparin (n=1,257).

**Study 11356 (RECORD 3):** A prospective, randomized, double-blind, double-dummy, parallel-group, active-comparator controlled, multicenter, multinational study designed to assess the efficacy and safety of Rivaroxaban 10 mg once daily dosing in the prevention of VTE in male and female subjects aged 18 years or above undergoing elective TKR. A total of 2,531 subjects were randomized to either Rivaroxaban group (n=1,254) or Enoxaparin (n=1,275).

**Study 11357 (RECORD 2):** A prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national design to compare the efficacy and safety of VTE prophylaxis with Rivaroxaban 10 mg once daily administered for 5 weeks to Enoxaparin 40 mg once daily administered for 10-14 days followed by placebo in men and women aged 18 years or above undergoing elective THR. A total of 3,148 subjects were randomized to either Rivaroxaban group (n=1,584) or Enoxaparin (n=1,564).

For all of the four Phase III studies, the primary efficacy endpoint was a composite of incidences of any DVT (proximal and/or distal DVT that were asymptomatic or symptomatic), non-fatal PE, or all cause death. The major secondary efficacy endpoints included the incidence of major VTE, incidence of DVT, incidence of symptomatic VTE, net clinical benefit.

The efficacy analysis was based on modified intent-to-treat (MITT) population which consisted of subjects who were valid for safety analysis, had undergone the appropriate surgery, and had an adequate assessment of thromboembolism. The safety analysis population was included all randomized subjects with receiving at least 1 dose of study medication.

The overall clinical program for Rivaroxaban includes a total of 17,852 subjects who participated in 64 completed studies and contributed safety data. Safety data from 11,281 subjects in 8 ongoing studies have been analyzed. These studies focus on the indications of secondary prevention of cardiovascular events after acute coronary syndrome, secondary prevention and long-term treatment of DVT and PE, stroke prevention in atrial

fibrillation, and prophylaxis of DVT and PE in hospitalized medically ill patients. An additional study in congestive heart failure (CHF) is ongoing.

### 1.3 Statistical Issues and Findings

1. There are some issues and findings in the bleeding analyses.

   Sponsor used Cox model for time to first event for bleeding analyses, although bleeding events are time dependent with multiple observations per subject and it is more appropriate to use time-to-event data in the multiple event setting. In this review, the Andersen-Gill (AG) formulation of the proportional hazards model as a counting process is used for the assessment of benefit in terms of bleeding. The results from these analyses are given in Section 3.2 and demonstrate that for patients following THR and TKR surgery, administration of Rivaroxaban for prophylaxis of DVT and PE increases the incidence of bleeding in comparison with the active control Enoxaparin, based on the results from categories of major bleeding alone or combined with surgical site or non-major clinically relevant bleeding as assessed by the Bleeding Event Adjudication Committee (AC/BE). It is known (from the label) that the most common side effect associated with using Enoxaparin is the risk of bleeding. The evidence that administration of Rivaroxaban could lead to bleeding events in significantly more patients relative to Enoxaparin amplifies this safety concern for Rivaroxaban in comparison to placebo in the setting of prophylaxis of DVT and PE following THR or TKR surgery.

2. Two of the four phase III RECORD studies were not appropriate for the US clinical use of the comparator drug Enoxaparin. RECORD 3 trial used a lower regimen not approved for Enoxaparin in US for TKR, whereas RECORD 2 used shorter duration of treatment in Enoxaparin group. Data from these trials are likely to have resulted in underestimation of Enoxaparin's treatment effect.

3. All RECORD study protocols included several secondary efficacy endpoints. However the study statistical analysis plans or SAPs did not include strong control of Type I error rate for confirmatory evidence of benefit based on secondary endpoints. A clinically important endpoint in these patient populations is Symptomatic VTE or Death. However nominal p-values for this secondary endpoints were <0.05 only for RECORD 2 and RECORD 3 studies which used shorter duration of treatment in RECORD 2 and used unapproved lower Enoxaparin regimen in RECORD 3 study. Data from these trials are likely to have resulted in underestimation of Enoxaparin's benefit in terms of Symptomatic VTE or death (Table 1).

**Table 1 Results for Symptomatic VTE or Death by individual study**

| RECORD | Rivaroxaban | Enoxaparin | Hazard Ratio (95% CI) |
|---|---|---|---|
| 1 | 10/2209<br>0.45% | 15/2224<br>0.67% | 0.7<br>(0.3, 1.5) |
| 2 | 5/1228<br>0.41% | 20/1229<br>1.6% | 0.2<br>(0.1, 0.7) |
| 3 | 8/1220<br>0.66% | 26/1239<br>2.1% | 0.3<br>(0.1, 0.7) |
| 4 | 12/1526<br>0.79 | 21/1508<br>1.4% | 0.6<br>(0.3, 1.2) |

Analysis results of major secondary endpoint for Pulmonary Thrombosis showed that in all four pivotal studies, the difference between Rivaroxaban group and Enoxaparin group was not statistically significant at 5% nominal level of significance. (Table 2).

**Table 2 P-value using fisher exact method for comparison of Rivaroxaban to Enoxaparin for PE.**

| Study | Pulmonary Thrombosis |
|---|---|
| RECORD 1 | P=0.69 |
| RECORD 2 | P=0.06 |
| RECORD 3 | P=0.12 |
| RECORD 4 | P=0.42 |

4. The sponsor analyzed these data from all 4 RECORD studies in an integrated analysis. When the statistical analysis plan for the integrated analysis was finalized to include all 4 record studies, the results from integrated data from record 1, 2 and 3 were known. Pooled exploratory analyses of these data are addressed in Section 5.1 in detail.

5. Baseline imbalances between the treatment groups were observed with respect to age, duration of surgery and current alcohol consumption in RECORD 1 study. Age and duration of surgery were reported to be risk factors for the primary efficacy variable and were identified as having a statistically significant effect by the exploratory logistic regression analysis. This result indicates that age and duration of surgery have an influence on VTE event. In RECORD 2, age and VTE risk levels were reported to be risk factors for the primary efficacy variable and there were identified as having a statistically significant effect by the exploratory logistic regression analysis. This result indicates that age and VTE risk levels have an influence on VTE event in RECORD 2 study.

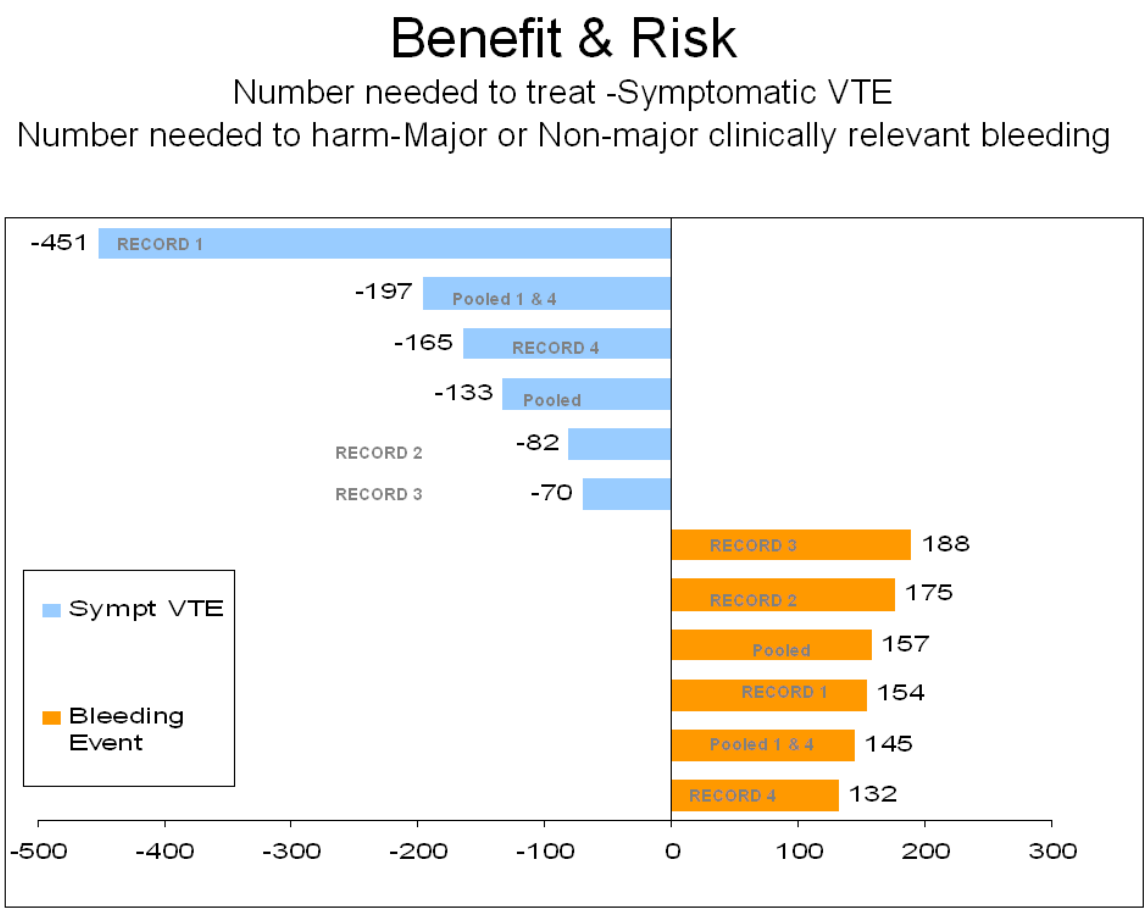
6. Baseline imbalances between the two treatments were also observed with respect to gender and thromboemblism risk factors in RECORD 3 study. Both of these were associated with a greater incidence of the primary efficacy variable in this study and there were a greater number of females and subjects with thromboembolism risk factors in the Rivaroxaban group as compared to the Enoxaparin. Exploratory logistic regression analyses were performed to assess the effect of baseline covariates. For the primary efficacy variable, none of the baseline covariates were identified as being statistically significant.

7. For the method of Mantel-Haenszel-weighted differences in proportions for the primary efficacy analysis, p-values were derived as the smallest significance level at which the hypothesis would be rejected for the given observation. As a consequence, the p-values might differ from those which would have resulted from applying Mantel-Haenszel test with no difference in proportion. This is due to the fact that for the calculation of the CI the estimated standard error is based on observed rates and not the hypothesized rates. In RECORD studies, the results are consistent between these methods.

8. In RECORD 4 Study, the MITT validity rate of 61% was lower than anticipated, although the rates were similar in the two treatment groups. Logistic regression analysis was performed, mainly to assess the effect of baseline covariates on the primary efficacy variable. Geographic region was selected as statistically significant. This result indicates that geographic region has an influence on VTE events.

9. The following figure (Figure 1) shows the results from benefit and risk assessment. Negative 451 from RECORD 1 study means that about one in every 451 patients will benefit from the Rivaroxaban group compared to the Enoxaparin group for RECORD 1 study. So RECORD 1 shows least benefit by using Rivaroxaban versus Enoxaparin. In contrast, negative 70 means that about one in every 70 patients will benefit from Rivaroxaban treatment compared to Enoxaparin. So RECORD 3 shows the most benefit of using Rivaroxaban. However, Record 3 study used unapproved lower Enoxaparin dose regimen. This result is consistent with the result from efficacy analysis. For the bleeding side effect, 132 means that about one in every 132 patients will be harmed by Rivaroxaban group relative to Enoxaparin for RECORD 4 study, and so on.

**Figure 1 Result for Benefit and Risk Assessment**



# 2. INTRODUCTION

## 2.1 Overview

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serous condition that is a common cause of mortality and morbidity. Subjects undergoing major orthopedic surgery, especially hip and knee surgery, are at a particularly high risk for asymptomatic DVT (incidence 40 to 60%) and symptomatic VTE (incidence 2 to 5%) without thromboprophylaxis. Prophylaxis with low-molecular-weight heparin (LMWH) is proven as efficacious therapy and is recommended as thromboprophylaxis.

The only currently available oral anticoagulant for prophylaxis of VTE after major orthopedic surgery in the U.S. is warfarin, vitamin K antagonists (VKA), characterized by a slow onset of action, variable response between subjects, need for frequent monitoring, interaction with drugs, and the complexity of supervision of dose adjustment.

Enoxaparin and other LMWHs provide effective and safe prophylaxis of VTE. However, they need to be administered subcutaneously, which is often associated with pain and subcutaneous bruising, and also with difficulty with compliance in the outpatient setting. Enoxaparin is the most widely used LMWH in hip and knee arthroplasty, with placebo-controlled studies showing about an 80% relative risk reduction in the incidence of VTE after both surgeries. The sponsor used Enoxaparin as the active comparator for the studies because it is indicated for prophylaxis after both THR and TKR surgery.

Rivaroxaban is a selective factor Xa inhibitor with oral availability. Factor Xa is at the common intersection of the extrinsic and the intrinsic pathways for thrombin formation. Selective inhibition of factor Xa by Rivaroxaban is expected to terminate the amplified burst of thrombin generation and may result in a better efficacy in inhibition of thrombus formation and safety profile.

The sponsor's NDA submission for Rivaroxaban included four Phase III and four Phase II studies for Agency review. All of the four Phase III pivotal studies were designed to be similar and identical in the efficacy and safety parameters measured. They were randomized, double-blinded, double-dummy, active-controlled, multinational studies using Rivaroxaban in the treatment of patient with VTE. For all of the four Phase III studies, the primary efficacy endpoint was a composite of incidences of any DVT (proximal and/or distal DVT that were asymptomatic or symptomatic), non-fatal PE, or all cause death. The major secondary efficacy endpoints included the incidence of major VTE, incidence of DVT, incidence of symptomatic VTE and net clinical benefit. The efficacy analysis was based on modified intent-to-treat (MITT) population which consisted of subjects who were valid for safety analysis, had undergone the appropriate surgery, and had an adequate assessment of thromboembolism. The safety analysis population was included all randomized subjects with receiving at least 1 dose of study medication. This statistical review report has focused on these four pivotal studies.

## 2.2 Data Sources

The sponsor submitted the clinical data and clinical study reports of the 4 Phase III and 4 Phase II studies. The data were to support the claim of using rivaroxaban for the indication of prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. Datasets for the studies were submitted electronically and were used in the review of these studies. These datasets can be found at the link of \\cdsesub1\evsprod\nda022406 \022406\0000\m5\datasets. Definitions of variables in the datasets and SAS codes were adequately documented.

# 3. STATISTICAL EVALUATION

This submission contains 4 randomized, double-blind, phase III comparative trials with Enoxaparin (RECORD1 [Study 11354], RECORD2 [Study 11357], RECORD3 [Study 11356], RECORD4 [Study11355]) to support the use of Rivaroxaban for the indication of prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery.

## 3.1 Evaluation of Efficacy

### 3.1.1 Study 11354 (RECORD 1)

#### 3.1.1.1 Study Design

This study was a prospective, randomized, active-comparator controlled, multi-center, and multinational study with a double-blind, parallel-group design. 4200 subjects were randomized to 1 of the following 2 treatment groups (2100 per treatment arm):

- 10 mg once daily of Rivaroxaban active substance plus a placebo syringe of Enoxaparin
- 1 placebo tablet of Rivaroxaban plus a syringe of Enoxaparin active substance at a dose of 40 mg

The study consisted of screening and randomization performed on Day 0, surgery (Day1), a treatment period (Days 0 through 35±4), a bilateral ascending venography (Day 36 ± 4, and a follow-up period (30 days [+5 days] after the last treatment with study drug). The time window for bilateral venography was eventually widened to Day 36 ± 6, the total duration of each subject's participation was up to 71 days.

#### 3.1.1.2 Study Objectives

The primary objective of the study was to assess the efficacy and safety of 10 mg Rivaroxaban once daily dosing in extended prevention of VTE in men and women with age ≥ 18 years undergoing elective total hip replacement.

#### 3.1.1.3 Definition of Efficacy and safety Endpoints

The primary efficacy endpoint for all 4 pivotal studies was incidences of DVT (proximal and/or distal), non-fatal PE, or all cause death.

The major secondary endpoint for the study was incidence of the composite endpoint comprising proximal DVT, non- fatal PE, and VTE-related death (referred to as "major VTE").

The main safety endpoint was for the study was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately.

### 3.1.1.4 Study Population results

***Disposition of Subjects***

In total, 4541 subjects were randomized at 218 study centers in 27 countries to treatment with either Rivaroxaban 10 mg (n=2,266) or Enoxaparin 40 mg (n=2,275). Table 3 summarizes the disposition of subjects. A total of 520 randomized subjects discontinued treatment prematurely (256 Rivaroxaban subject and 264 Enoxaparin subjects). The most common reason for discontinuation in both treatments was withdrawal of consent (5.2%) followed by adverse events (3.8%). The rates were similar between two treatment groups. There were 5 of 2,266 (0.2%) Rivaroxaban subjects vs 11 of 2,275 (0.5%) Enoxaparin subjects discontinued due to reaching the clinical endpoint, which were either reporting of a DVT or PE. All randomized subjects were to have entered the follow-up period, whether or not completing the treatment phase of the study. Of 4,135 subjects entering the follow-up period, 150 subjects prematurely terminated (77 of 2,074 Rivaroxaban subjects and 73 of 2061 Enoxaparin subjects). The most common reason for premature termination from the study during the follow-up period was loss to follow-up.

**Table 3 Reviewer's Summary of Patient Disposition for RECORD 1**

| Disposition Category | Number of Subjects, n (%) | | |
|---|---|---|---|
| | Rivaroxaban | Enoxaparin | Total |
| Prior to scheduled end of treatment | | | |
| All randomized subjects | 2266 | 2275 | 4541 |
| Safety Population | 2209 (98) | 2224 (98) | 4433 (98) |
| MITT Population | 1595 (70) | 1558 (69) | 3153 (69) |
| Completed study | 2010 (89) | 2011 (88) | 4021 (87) |
| Discontinued prematurely | 256 (11.3) | 264 (11.6) | 520 (11.5) |
| Adverse event | 82 (3.6) | 92 (4.0) | 174 (3.8) |
| Death | 1 (<0.1) | 2 (<0.1) | 3 (<0.1) |
| Follow-up | | | |
| Entered follow-up period | 2074 | 2061 | 4135 |
| Discontinued prematurely | 77(3.7) | 73(3.5) | 150 (3.6) |
| Adverse event | 9 (0.4) | 3 (0.1) | 12 (0.3) |
| Death | 1 (<0.1) | 0 | 1 (<0.1) |

***Demographics and Other Baseline Characteristics***

Table 4 shows the reviewer's summary of test on demographic characteristics for modified intent to treat analysis population. It shows that the distributions were similar between two treatment groups for sex, race, age, weight, BMI group based on MITT

population. However, there was between group differences in patient distribution of baseline alcohol consumption.

**Table 4 Reviewer's Summary of Homogeneity tests conducted on Demographic Characteristics (MITT Population) RECORD 1**

| Demographic Characteristic n=3153 (%) | Test | P-value |
|---|---|---|
| Sex: Female 1698 (53.9)<br>Male 1455 (46.1) | Cochran-Mantel-Haenszel | 0.56 |
| Race: White 2943 (93.3)<br>Black 24 (0.8)<br>Asian 4 (0.1)<br>American Indian 4 (0.1)<br>Hispanic 23 (0.7) | Cochran-Mantel-Haenszel | 0.78 |
| Age: 18-40 Yrs 126 (4.0)<br>>40-<65 Yrs 1519 (48.2)<br>65-75 Yrs 1148 (36.4)<br>>75 Yrs 360 (11.4) | ANOVA | 0.17 |
| Weight (KG) | ANOVA | 0.82 |
| Current Alcohol Consumption:<br>Abstinent 1313 (41.6)<br>Light 1566 (49.7)<br>Moderate 260 (8.3)<br>Heavy 3 (0.1) | Cochran-Mantel-Haenszel | 0.004 |

### 3.1.1.5 Primary Efficacy Analyses Methods and Results

The primary efficacy endpoint was a composite of any DVT (proximal and/or distal), nonfatal PE, and death from all causes. For the primary efficacy variable, the PP population was the primary population used for the test for non-inferiority of Rivaroxaban as compared to Enoxaparin and the MITT population was the primary population used for the test for superiority of Rivaroxaban as compared to Enoxaparin in the event that the PP analyses established non-inferiority. The incidence rates of the primary efficacy endpoint and its individual components are summarized in Table 3. Table 4 presents the point estimates and the corresponding 95% CIs for the comparison of Rivaroxaban with Enoxaparin with regard to the primary efficacy endpoint in the PP and MITT population. A statistically significant difference ($p<0.001$) for PP analysis demonstrated the non-inferiority of Rivaroxaban over Enoxaparin in preventing VTE; a statistically significant difference ($p<0.001$) demonstrated the superiority of Rivaroxaban over Enoxaparin in preventing VTE (Table 5, Table 6)

**Table 5 Summary of Incidence of Primary Efficacy Endpoint (RECORD 1)**

| Primary efficacy endpoint | PP Population | | MITT Population | |
|---|---|---|---|---|
| | Rivaroxaban (N=1537) n(%) | Enoxaparin (N=1492) n(%) | Rivaroxaban (N=1537) n(%) | Enoxaparin (N=1492) n(%) |
| Any event (any cause) | 13 (0.9) | 50 (3.4) | 18 (1.1) | 58 (3.7) |
| Death | 1 (<0.1) | 2 (0.1) | 4 (0.3) | 4 (0.3) |
| Nonfatal PE | 2 (0.1) | 1 (<0.1) | 4 (0.3) | 1 (<0.1) |
| DVT | 11 (0.7) | 47 (3.2) | 12 (0.8) | 53 (3.4) |
| Components | | | | |
| Death (VTE related) | 0 | 1 (<0.1) | 0 | 1(<0.1) |
| Death (not VTE related) | 0 | 1 (<0.1) | 2(0.1) | 3(0.2) |
| Death (unexplained) | 1(<0.1) | 0 | 2(0.1) | 0 |
| DVT, proximal | 0 | 27 | 1(<0.1) | 31 (2.0) |
| DVT, distal | 11(0.7) | 24 | 12(0.8) | 27 (1.7) |

**Table 6 Point Estimate of Treatment Difference and 95% Confidence Intervals (RECORD 1)**

| Endpoint | Treatment | point estimate [95% CI] using exact method | Point estimate (95% CI ) using Mantel-Haenszel-weighted difference | P-value Ho: Diff>3.5% Diff=0% |
|---|---|---|---|---|
| PP Population | Rivaroxaban | 0.85% [0.45%, 1.44%] | -2.53% [-3.55%, -1.51%] | <0.001 |
| | Enoxaparin | 3.35% [2.5%, 4.39%] | | |
| | | | | |
| MITT Population | Rivaroxaban | 1.13% [0.67%, 1.78%] | -2.68% [-3.70%, -1.65%] | <0.001 |
| | Enoxaparin | 3.72% [2.84%, 4.78%] | | |

The sponsor also conducted sensitivity analyses. All analyses indicated statistical superiority of the Rivaroxaban group as compared to the Enoxaparin by applying varying scenarios for handling of missing responses due to inadequate assessment of thromboembolism.

### 3.1.1.6 Major Secondary Efficacy Analysis

Table 7 shows the summarized the incidence of major VTE for the major secondary efficacy analysis.

**Table 7 Summary of Incidence Rates of Major VTE for Major Secondary Efficacy Endpoint (RECORD 1)**

| Endpoint components | PP Population | | MITT Population | |
|---|---|---|---|---|
| | Rivaroxaban (N=1622) n(%) | Enoxaparin (N=1604) n(%) | Rivaroxaban (N=1686) n(%) | Enoxaparin (N=1678) n(%) |
| Major VTE | 2 (0.12) | 29 (1.81) | 4 (0.24) | 33 (1.97) |
| Death (VTE related) | 0 (0.0) | 1 (0.06) | 0 | 1 (0.06) |
| Nonfatal PE | 2 (0.12) | 1 (0.06) | 4 (0.24) | 1 (0.06) |
| DVT | 0 (0.0) | 27 (1.68) | 1 (0.06) | 31 (1.85) |

Table 8 shows the summary of point estimates and corresponding 95% CIs for the pair-wise comparisons of Rivaroxaban vs Enoxaparin with regard to major VTE in the PP and MITT populations. For the PP and MITT populations, the incidence rate of major VTE in the Enoxaparin group was more than 14 times and 8 times, respectively, the rate observed in the Rivaroxaban group. For the component 'nonfatal PE', incidence were 2 vs 1 (PP population) and 4 vs 1 (MITT population) comparing the Rivaroxaban group with the Enoxaparin group. For both populations, the upper limit of the 95% CI for the Mantel-Haenszel-wighted treatment difference (Rivaroxaban minus Enoxaparin) was below 0, thereby establishing not only non-inferiority (based on the non-inferiority margin of 1.5%) but also superiority of Rivaroxaban over Enxaparin.

**Table 8 Point Estimates and Corresponding 95% CIs of Between-Group Difference of Major VTE (RECORD 1)**

| Endpoint | Treatment | point estimate [95% CI] using exact method | Point estimate (95% CI ) using Mantel-Haenszel-weighted difference | P-value Ho: Diff>1.5% Diff=0% |
|---|---|---|---|---|
| PP Population | Rivaroxaban | 0.12% [0.01%, 0.4%] | -1.69% [-2.37%, -1.02%] | <0.001 |
| | Enoxaparin | 1.8% [1.2%, 2.6%] | | |
| | | | | |
| MITT Population | Rivaroxaban | 0.24% [0.06%, 0.61%] | -1.74% [-2.45%, -1.03%] | <0.001 |
| | Enoxaparin | 1.97% [1.36%, 2.75%] | | |

The following table (Table 9) summarizes the secondary efficacy endpoint for DVT, PE and Symptomatic VTE. The 95% CIs for the difference to Enoxaparin are presented using exact method. Based upon the 95% CIs, Deep vein thrombosis showed superiority of Rivaroxaban to Enoxaparin. The secondary endpoint of Pulmonary embolism and Symptomatic VTE were not statistical significant between Rivaroxaban group and Enoxaparin group.

**Table 9 Summary of Secondary Efficacy Endpoint for DVT, PE and Symptomatic VTE (MITT Population) (REECORD 1)**

| Endpoint | Rivaroxaban N=1595 | Enoxaparin N=1558 | 95% CI Difference to Enoxaparin |
|---|---|---|---|
| Deep vein thrombosis | 12(0.8) | 53 (3.4) | (-3.67, -1.68) |
| Pulmonary embolism | 4 (0.3) | 2 (0.1) | (-0.24, 0.52) |
| Symptomatic VTE | 6 (0.4) | 11 (0.7) | (-0.92, 0.21) |

#### 3.1.1.8 Efficacy Conclusions for RECORD 1

Based on the non-inferiority (margin of 3.5%) test using PP population, results for the composite primary efficacy endpoint demonstrated that the objective of non-inferiority against Enoxaparin was met.

Analysis using PP population and MITT population for the primary efficacy endpoint showed the superiority of Rivaroxaban over Enoxaparin in preventing VTE.

Analysis for the major secondary endpoint of Major VTE showed superiority of Rivaroxaban over Enoxaparin. Deep vein thrombosis showed superiority of Rivaroxaban to Enoxaparin. The secondary endpoint of Pulmonary embolism and Symptomatic VTE were not statistically significant between Rivaroxaban group and Enoxaparin group.

### 3.1.2 Study 11357 (RECORD 2)

#### 3.1.2.1 Study Design

This study was a prospective, randomized, active-comparator controlled, multi-center, and multinational study with a double-blind, parallel-group design. 2500 subjects were randomized to 1 of the following 2 treatment groups (1250 per treatment arm):

- VTE prophylaxis with Rivaroxaban 10 mg od administrated for 5 weeks (35 days ± 4 days)
- VTE prophylaxis with Enoxaparin 40 mg once daily administered for 10-14 days ( 12 days ± 2 days ) followed by placebo up to day 35.

The active treatment period for the Enoxaparin arm was Day 0 (evening before surgery) to Day 12± 2 (evening before Day 13 visit). Rivaroxaban placebo was taken from Day 1 (at least 6-8 h after wound closure) until Day 35 ± 4 (evening before venography). The Rivaroxaban arm was from Day 1 (at least 6-8 h after wound closure) until Day 35 ± 4 (evening before venography) with the application of Enoxaparin placebo from Day 0 until Day 12 ± 2 (evening prior Day 13 visit). Because of shorter duration of treatment for Enoxaparin group, this study may underestimate of Enoxaparin effect.

### 3.1.2.2 Study Objectives

The primary objective of the study was to compare the efficacy and safety of VTE prophylaxis with Rivaroxaban 10 mg once daily administered for 5 weeks to Enoxaparin 40 mg once daily administered for 10-14 days followed by placebo in men and women aged 18 years or above undergoing elective total hip replacement.

### 3.1.2.3 Study Population

The study population consisted of male and female subjects aged 18 years or above undergoing elective total hip replacement.

### 3.1.2.4 Definition of Efficacy and safety Endpoints

The primary endpoint for the study was a composite endpoint of any DVT (proximal and/or distal), non-fatal PE, and death from all causes (same as RECORD 1)

The major secondary endpoint for the study was incidence of the composite endpoint comprising proximal DVT, non- fatal PE, and VTE-related death (referred to as "major VTE") (same as RECORD 1).

The main safety endpoint was for the study was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately (same as RECORD 1).

### 3.1.2.5 Study Population results

***Disposition of Subjects***

In total, 2,509 subjects were randomized at 123 study centers in 21 countries to treatment with either Rivaroxaban 10 mg once daily (n=1,252) or Enoxaparin 40 mg once daily (n=1,257). Table 10 shows the summarized the disposition of subjects. A total of 300 randomized subjects discontinued treatment prematurely (135 Rivaroxban subjects and 165 Enoxaparin subjects). The most common reason for discontinuation in both treatments was withdrawal of consent (4.1% Rivaroxaban subjects vs 4.1% Enoxaparin subjects) followed by adverse events (3.5% vs 4.3%). There were 3 of 1,252 (0.2%) Rivaroxaban subjects' vs 13 of 1,257 (1.0%) Enoxaparin subjects discontinued due to reaching the clinical endpoint, which were either reporting of a DVT or PE. All randomized subjects were to have entered the follow-up period, whether or not completing the treatment phase of the study. Of 2,286 subjects entering the follow-up period, 68 subjects prematurely terminated (40 of 1,148 [3.5%] Rivaroxaban subjects and 28 of 1,138 Enoxaparin). The most common reason for premature termination from the study during the follow-up period was loss to follow-up (28 of 1148 [2.4%] Rivaroxaban subjects and 17 of 1138 [1.5%] Enoxaparin subjects).

**Table 10 Reviewer's Summary of Patient Disposition for RECORD 2**

| Disposition Category | Number of Subjects, n (%) | | |
|---|---|---|---|
| | Rivaroxaban | Enoxaparin | Total |
| Prior to scheduled end of treatment | | | |
| All randomized subjects | 1252 | 1257 | 2509 |
| Safety Population | 1228 (98) | 1229 (98) | 2457 (98) |
| MITT Population | 864 (69) | 869 (69) | 1733 (69) |
| Completed study | 1117 (89) | 1092 (87) | 2209 (88) |
| Discontinued prematurely<br>Adverse event<br>Death | 135 (11)<br>44 (3.5)<br>1 (<0.1) | 165 (13)<br>54 (4.3)<br>3 (<0.1) | 300 (12)<br>98 (3.9)<br>4 (<0.1) |
| Follow-up | | | |
| Entered follow-up period | 1148 | 1138 | 2286 |
| Discontinued prematurely<br>Adverse event<br>Death | 40 (3.5)<br>5 (0.4)<br>1 (<0.1) | 28(2.5)<br>4 (0.4)<br>1 (<0.1) | 68 (3.0)<br>9 (0.4)<br>2 (<0.1) |

***Demographics and Other Baseline Characteristics***

The following table shows the reviewer's summary of homogeneity test on demographic characteristics for modified intent to treat analysis population (Table 11). The resulted showed that are no statistically significant different between subgroup of sex, race, age, weight, BMI and alcohol consumption group for MITT population.

**Table 11 Summary of Homogeneity tests conducted on Demographic Characteristics (MITT Population) (RECORD 2)**

| Demographic Characteristic N=1924 (%) | Test | P-value |
|---|---|---|
| Sex: Female 696 (36.2)<br>Male 1228 (63.8) | Cochran-Mantel-Haenszel | 0.51 |
| Race: White 1354 (70.4)<br>Black 90 (4.7)<br>Asian 305 (15.8)<br>American Indian 4 (0.2)<br>Hispanic 168 (8.7) | Cochran-Mantel-Haenszel | 0.92 |
| Age: 18-40 Yrs 22 (1.1)<br>>40-<65 Yrs 900 (46.8)<br>65-75 Yrs 728 (37.8)<br>>75 Yrs 274 (14.2) | ANOVA | 0.83 |
| Weight (KG) | ANOVA | 0.18 |

### 3.1.2.5 Primary Efficacy Analyses Methods and Results

The primary efficacy endpoint was the composite of any DVT (proximal and/or distal), nonfatal PE, and death from all causes. The incidence rates of the primary efficacy endpoint and its individual components are summarized in Table 12. Table 13 presents the point estimates and the corresponding 95% CIs for the comparison of Rivaroxaban with Enoxaparin with regard to the primary efficacy endpoint in the PP and MITT population. The primary efficacy population was the MITT population for superiority testing, and the analysis of the PP population was performed as supportive analysis. A statistically significant difference ($p<0.001$) for MITT analysis demonstrated the superiority of a 5 week Rivaroxaban over a 2 week Enoxaparin in the prevention of VTE in this subject population. A statistically significant difference ($p<0.001$) for the PP analysis also demonstrate the superiority of the 5 week over the 2 weeks Enoxaparin in preventing VTE in hip replacement surgery.

**Table 12 Summary of Incidence of Primary Efficacy Endpoint (RECORD 2)**

| Primary efficacy endpoint | PP Population | | MITT Population | |
|---|---|---|---|---|
| | Rivaroxaban (N=812) n(%) | Enoxaparin (N=803) n(%) | Rivaroxaban (N=864) n(%) | Enoxaparin (N=869) n(%) |
| Any event (any cause) | 11 (1.4) | 66 (8.2) | 17 (2.0) | 81 (9.3) |
| Death | 1 (0.1) | 2 (0.3) | 2 (0.2) | 6 (0.7) |
| Nonfatal PE | 0 | 3 (0.4) | 1 (0.1) | 4 (0.5) |
| DVT | 10 (1.2) | 61 (7.6) | 14 (1.6) | 71 (8.2) |
| Components | | | | |
| Death (VTE related) | 0 | 1 (<0.1) | 0 | 1(<0.1) |
| Death (not VTE related) | 0 | 1 (<0.1) | 0 | 4(0.5) |
| Death (unexplained) | 1(<0.1) | 0 | 2(0.2) | 1 (0.1) |
| DVT, proximal | 3 (0.4) | 37 (4.6) | 5 (0.6) | 44 (5.1) |
| DVT, distal | 8 (1.0) | 44 (5.5) | 11(1.3) | 49 (5.6) |

**Table 13 Point Estimate of Treatment Difference and 95% Confidence Intervals (RECORD 2)**

| Endpoint | Treatment | point estimate [95% CI] using exact method | Point estimate (95% CI ) using Mantel-Haenszel-weighted difference | P-value Ho: Diff>3.5% Diff=0% |
|---|---|---|---|---|
| PP Population | Rivaroxaban | 1.35% [0.68%, 2.41%] | -6.8% [-8.85%, -4.75%] | <0.001 |
| | Enoxaparin | 8.22% [6.41%, 10.34%] | | |
| | | | | |
| MITT Population | Rivaroxaban | 1.97% [1.15%, 3.13%] | -7.28% [-9.41%, -5.15%] | <0.001 |
| | Enoxaparin | 9.32% [7.47%, 11.45%] | | |

The sponsor also conducted sensitivity analyses. All analyses indicated statistical superiority of the Rivaroxaban group as compared to the Enoxaparin by applying varying scenarios for handling of missing responses due to not adequate assessment of thromboembolism.

#### 3.1.2.6 Secondary efficacy analysis

The following table shows the summarized the incidence of major VTE (Table 14). For the PP and MITT populations, the incidence rate of major VTE in the Enoxaparin 40 mg od group was approximately 14 times and 8 times respectively, the rate observed in the Rivaroxaban 10 mg od group. For the component "nonfatal PE". Incidence rates were 0 vs 0.3% for the PP population and 0.1% vs 0.4% (MITT population) comparing the Rivaroxaban 10 mg od group with the Enoxaparin 40 mg od group.

**Table 14 Incidence Rates of Major VTE for Major Secondary Efficacy Endpoint for MITT Population (RECORD 2)**

| Endpoint components | PP Population | | MITT Population | |
|---|---|---|---|---|
| | Rivaroxaban (N=898) n(%) | Enoxaparin (N=884) n(%) | Rivaroxaban (N=961) n(%) | Enoxaparin (N=962) n(%) |
| Major VTE | 3 (0.3) | 41 (4.6) | 6 (0.6) | 49 (5.1) |
| Death (VTE related) | 0 (0.0) | 1 (0.1) | 0 | 1 (0.1) |
| Nonfatal PE | 0 (0.0) | 3 (0.3) | 1 (0.1) | 1 (0.4) |
| DVT | 3 (0.3) | 37 (4.2) | 5 (0.5) | 44 (4.6) |

The following table shows the summary of point estimates and corresponding 95% CIs for the pair-wise comparisons of Rivaroxaban 10 mg od with Enoxaparin 40 mg od with regard to major VTE in the PP and MITT populations (Table 15). For both populations, the upper limit of the 95% CI for the Mantel-Haenszel-weighted treatment difference was below 0, thereby establishing superiority of Rivaroxaban over Enoxaparin.

**Table 15 Point Estimates and Corresponding 95% CIs of Between-Group Difference of Major VTE (RECORD 2)**

| Endpoint | Treatment | point estimate [95% CI] using exact method | Point estimate using Mantel-Haenszel-weighted difference | P-value Ho: Diff>1.5% Diff=0% |
|---|---|---|---|---|
| PP Population | Rivaroxaban | 0.33% [0.07%, 0.97%] | -4.31% | <0.001 |
| | Enoxaparin | 1.8% [1.2%, 2.6%] | | |
| | | | | |
| MITT Population | Rivaroxaban | 0.62% [0.23%, 1.35%] | -4.49% | <0.001 |
| | Enoxaparin | 5.09% [3.79%, 6.68%] | | |

The following table (Table 16) shows reviewer's summary of secondary efficacy endpoint for DVT, PE and Symptomatic VTE. Pulmonary embolism does not show statistically significant between Rivaroxaban group and Enoxapaparin group.

**Table 16 Summary of Secondary efficacy Endpoint (MITT Population) (RECORD 2)**

| Endpoint | Rivaroxaban N=864 | Enoxaparin N=869 | 95% CI Difference to Enoxaparin |
|---|---|---|---|
| Deep vein thrombosis | 14(1.6) | 71 (8.2) | (-8.48, -4.48) |
| Pulmonary embolism | 1 (0.1) | 5 (0.6) | (-1.23, 0.15) |
| Symptomatic VTE | 3 (0.4) | 15 (1.7) | (-2.50, -0.37) |

#### 3.1.2.8 Efficacy Conclusions for RECORD 2

The primary efficacy endpoint was obtained from the MITT population which comprised 1733 subjects of the 2509 randomized subjects. The composite primary efficacy endpoint occurred in 17 (2.0%) and 81 (9.3) of subjects randomized to Rivaroxaban or Enoxaparin, respectively; the results showed the superiority of Rivaroxaban over Enoxaparin in preventing VTE

All components of the primary composite efficacy endpoint were reduced in the Rivaroxaban group compared with the Enoxaparin group.

For the major VTE of secondary endpoint, the Rivaroxaban was statistically superior to the Enoxaparin.

For Symptomatic VTE the Rrivaroxaban was statistically superior to the Enoxaparin. For Pulmonary embolism, the Rivaroxaban was not statistically superior to the Enoxaparin.

### 3.1.3 Study 11356, 11355 (RECORD 3, RECORD 4)

#### 3.1.3.1 Study Design

RECORD 3 and RECORD 4 were designed to be similar in methodology and identical in the efficacy and safety parameters measured. These studies were multicenter (RECORD 3; 147 sites. RECORD 4; 130 sites), randomized, double-blind, active comparator controlled, double-dummy, parallel group trials designed to compare the efficacy and safety of Rivaroxaban with Enoxaparin. In each study, treatment with Rivaroxaban was 10 mg od for ±2 days, and treatment with Enoxaparin s.c. was either 40 mg od for 13±2 days (RECORD 3) or 30 mg bid for 12±2 days (RECORD 4) for the prevention of VTE in subjects undergoing elective TKR surgery.

- Record 3-Short-term prevention of VTE until Day 12±2;

Administration of 40 mg od Enoxaparin (beginning before surgery on day 0) and administration of 10 mg od Rivaroxaban (beginning after surgery on Day1). RECORD 3 used lower dose of Enoxaparin that is not approved in the US. As a result, this study was conducted entirely outside US. This control regimen could potentially lead to an under-estimation of the Enoxaparin effect.

- Record 4-Short-term prevention of VTE until Day 12±2;

Administration of 30 mg bid Enoxaparin (beginning after surgery on day 1-2) and administration of 10 mg od Rivaroxaban.

The studies consisted of screening and randomization performed on Day 0, surgery (Day 1) and a treatment period from Day 0 through Day 35 ± 4 or Day 12 ± 2 for record 1 and 2 or record 3 and 4, respectively. Dosing with Enoxaparin 40 mg od (or matching placebo injection) in record 1, 2 and 3 started prior to surgery. In record 4 dosing was Enoxaparin 30 mg bid (or matching placebo) started after surgery. For Rivaroxaban 10 mg od (or matching placebo), the first dose was to be given 6 to 8 hours after wound closure on day 1. In the total hip-replacement (THR) studies record 1 and 2 Rivaroxaban was given until Day 35 ± 4 in record 1 and until Day 12 ± 2 followed by placebo RECORD 2. In the total knee-replacement (TKR) studies 11355 (RECORD 4) and 11356 (RECORD 3) both Rivaroxaban and Enoxaparin were administered until day 12 ± 2.

### 3.1.3.2 Definition of Analysis Population

- The safety analysis population consisted of subjects who were randomized and received at least 1 dose of study medication and was used for all integrated analyses of symptomatic events.
- The modified intent-to-treat (MITT) population consisted of subjects who were valid for safety analysis and additionally had undergone the appropriate surgery and had an adequate assessment of thromboemblism. The MITT population was used for superiority test in each of the individual Record studies and for subgroup analysis of the pooled data.
- Per Protocol population: modified ITT plus had stronger evaluable for any (or proximal) VTE and no major protocol violations

### 3.1.3.3 Definition of Efficacy and safety Endpoints

The primary endpoint in each of the individual Record 3 and Record was the incidence of total VTE that was defined as composite of any DVT, non-fatal PE, or all cause death.

The major secondary endpoint for the study was incidence of the composite endpoint comprising proximal DVT, non- fatal PE, and VTE-related death (referred to as “major VTE”).

The main safety endpoint was for the study was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately.

### 3.1.3.4 Study Population results

***Disposition of Subjects***

In RECORD 3, 2531 subjects were randomized and 2459 subjects received at least one dose of blinded study medication. In RECORD 4, 3148 subjects were randomized and 3034 subjects received at least one dose of blinded medication (Table 17).

**Table 17 Subject Populations for RECORD 3 and RECORD 4**

| Study | Rivaroxaban n (%) | Enoxaparin n (%) | Total n(%) |
|---|---|---|---|
| Randomized<br>Record 3<br>Record 4 | <br>1254 (100)<br>1584 (100) | <br>1277 (100)<br>1564 (100) | <br>2532 (100)<br>3148 (100) |
| Safety<br>Record 3<br>Record 4 | <br>1220 (97)<br>1526 (96) | <br>1239 (97)<br>1508 (96) | <br>2459 (97)<br>3034 (96) |
| MITT<br>Record 3<br>Record 4 | <br>824 (66)<br>965 (61) | <br>878 (69)<br>959 (61) | <br>1702 (67)<br>1924 (61) |
| Per Protocol<br>Record 3<br>Record 4 | <br>793 (63)<br>864 (55) | <br>838 (66)<br>878 (56) | <br>1631 (64)<br>1742 (55) |

***Demographics and Other Baseline Characteristics***
The demographic and baseline characteristics of subjects in each of the 2 studies were generally balanced between the 2 treatment groups in the safety, MITT, and PP populations.

### 3.1.3.5 Primary Efficacy Analyses Methods and Results

In Record 3, analyses using the PP population showed a statistically significant ($p<0.001$) lower incidence in total VTE in the Rivaroxaban group than in the Enoxaparin group. Analyses using the MITT population also showed the same result with PP population. For both analysis populations, the upper limit of the two-sided 95% CI for the Mantel-Haenszel-weighted treatment difference was below 0, demonstrating superiority of Rivaroxaban over Enoxaparin (Table 20).

In RECORD 4, analysis using the PP population showed a statistically significant ($p=0.036$) lower incidence in total VTE in the Rivaroxaban group. MITT population also showed a statistically significant ($p=0.012$) lower incidence of total VTE in the Rivaroxaban group than in the Enoxaparin in preventing VTE. For both analysis populations, the upper limit of the two-sided 95% CI for the Mantel-Haenszel-weighted treatment difference was below 0, thereby establishing superiority of Rivaroxaban over Enoxaparin (Table 21).

For both RECORD 3 and RECORD 4, the incidence of all components of total VTE were reduced in the Rivaroxaban group versus the Enoxaparin group for both the MITT

and PP population (Table 18, Table 19). Sponsor stated that the overall reduction in total VTE was primarily due to decreases in both proximal and distal DVT since the incidence of the PE and death components were low for both treatments.

**Table 18 Incidence of Primary Efficacy Endpoint (Total VTE) and individual components for pp population**

| Study | RECORD 3 | | RECORD 4 | |
|---|---|---|---|---|
| endpoint | Rivaroxaban N=793 | Enoxaparin N=838 | Rivaroxaban N=864 | Enoxaparin N=879 |
| Total VTE | 74 (9.3) | 152 (18.1) | 58 (6.7) | 82 (9.3) |
| Components | | | | |
| Death (VTE-related) | 0 | 0 | 1 (0.1) | 0 |
| Death (not VTE-related) | 0 | 0 | 0 | 0 |
| Death, (unexplained) | 0 | 2 (0.2) | 0 | 2 (0.2) |
| DVT, proximal | 9 (1.1) | 19 (2.3) | 8 (0.9) | 11 (1.3) |
| DVT, distal | 69 (8.7) | 143 (17.1) | 51 (5.9) | 72 (8.2) |

**Table 19 Incidence of Primary Efficacy Endpoint (Total VTE) and individual components for MITT population**

| Study | RECORD 3 | | RECORD 4 | |
|---|---|---|---|---|
| endpoint | Rivaroxaban N=824 | Enoxaparin N=878 | Rivaroxaban N=965 | Enoxaparin N=959 |
| Total VTE | 79 (9.6) | 166 (18.9) | 67 (6.9) | 97 (10.1) |
| Components | | | | |
| Death (VTE-related) | 0 | 0 | 1 (0.1) | 0 |
| Death (not VTE-related) | 0 | 0 | 1 (0.1) | 0 |
| Death, (unexplained) | 0 | 2 (0.2) | 0 | 3 (0.3) |
| DVT, proximal | 9 (1.1) | 20 (2.3) | 8 (0.8) | 14 (1.5) |
| DVT, distal | 74 (9) | 156 (17.8) | 57 (5.9) | 82 (8.6) |

**Table 20 Reviewer's summary of pair-wise comparisons and 95% confidence intervals for the primary efficacy endpoint (RECORD 3)**

| Endpoint | Treatment | point estimate [95% CI] using exact method | Point estimate (95% CI ) using Mantel-Haenszel-weighted difference | P-value Ho: Diff>3.5% Diff=0% |
|---|---|---|---|---|
| PP Population | Rivaroxaban | 9.33%[7.4%, 11.6%] | -8.7 [-12%, -5%] | <0.001 |
| | Enoxaparin | 18.1% [15.6%, 20.9%] | | |
| | | | | |
| MITT Population | Rivaroxaban | 9.6% [7.7%, 11.78%] | -9.15% [-12.4%, -5.9%] | <0.001 |
| | Enoxaparin | 18.9% [16.4%, 21.7%] | | |

**Table 21 Reviewer's summary of pair-wise comparisons and 95% confidence intervals for the primary efficacy endpoint (RECORD 4)**

| Endpoint | Treatment | point estimate [95% CI] using exact method | Point estimate (95% CI ) using Mantel-Haenszel-weighted difference | P-value Ho: Diff>3.5% Diff=0% |
|---|---|---|---|---|
| PP Population | Rivaroxaban | 6.7%[5.14%, 8.6%] | -2.7 [-5.3%, -0.17%] | P=0.036 |
| | Enoxaparin | 9.3% [7.5%, 11.5%] | | |
| | | | | |
| MITT Population | Rivaroxaban | 6.9% [5.4%, 8.7%] | -3.2% [-5.7%, -0.71%] | P=0.012 |
| | Enoxaparin | 10.11% [8.3%, 12.2%] | | |

The sponsor also conducted sensitivity analyses. All analyses indicated statistical superiority of the Rivaroxaban group as compared to the Enoxaparin by applying varying scenarios for handling of missing responses in the subjects invalidate due to inadequate assessment of thromboembolism.

### 3.1.3.6 Analysis of Potential Risk Factors

The following table shows exploratory logistic regression with a stepwise variable selection process of the baseline covariates using an entry significance lever of 5% (Table 22) for RECORD 3. The treatment group was included in the model as fixed term. Region was selected as statistically significant for MITT population. This result indicates that Geographic region has an influence on VTE events.

**Table 22 Logistic regression analysis of the primary efficacy endpoint for MITT population (RECORD 3)**

| Explanatory variables | P-value | Comparison the odds ratio is estimated for | Odds ratio | 95% CI |
|---|---|---|---|---|
| Treatment group | <0.0001 | Rivaroxaban vs Enoxaparin | 0.451 | [0.337, 0.603] |
| Gegraphic Region | <0.0001 | | | |

### 3.1.3.7 Secondary Efficacy Endpoint for RECORD 3 and RECORD 4

In RECORD 3, analyses for major VTE using the PP population showed a statistically significant (p=0.025) lower incidence of major VTE in the Rivaroxaban group than in the Enoxaparin group. Analysis using MITT population valid for major VTE showed a statistically significant (p=0.01) lower incidence in major VTE in the Rivaroxaban group. For both populations, the upper limit of the two-sided 95% CI for the Mantel-Haeszel-weighted treatment difference was below 0, thus, Rivaroxaban was superior to Enoxaparin in preventing major VTE (Table 25).

In RECORD 4, analyses for major VTE using the pp and MITT population showed that the upper limit of the two –sided 95% CI for the Mantel-Haenszel-weighted treatment difference showed a lower incidence of major VTE in the Rivaroxaban group; but this difference did not reach statistical significance (Table 26).

**Table 23 Main Secondary Efficacy Endpoint (Major VTE) for PP population**

| Study | RECORD 3 | | RECORD 4 | |
|---|---|---|---|---|
| endpoint | Rivaroxaban N=874 | Enoxaparin N=891 | Rivaroxaban N=1011 | Enoxaparin N=1020 |
| Major VTE | 9(1.0) | 22 (2.5) | 11 (1.1) | 15 (1.5) |
| Death (VTE-related) | 0 | 0 | 1 (0.1) | 0 |
| Nonfatal PE | 0 | 3 | 3 0.3) | 4 (0.4) |
| DVT, Proximal | 9 (1.0) | 19 (2.1) | 8 (0.8) | 11 (1.1) |

**Table 24 Main Secondary Efficacy Endpoint (Major VTE) for MITT population**

| Study | RECORD 3 | | RECORD 4 | |
|---|---|---|---|---|
| endpoint | Rivaroxaban N=908 | Enoxaparin N=925 | Rivaroxaban N=1122 | Enoxaparin N=1112 |
| Major VTE | 9(1.0) | 24 (2.6) | 13 (1.2) | 22 (2.0) |
| Death (VTE-related) | 0 | 0 | 1 (0.1) | 0 |
| Nonfatal PE | 0 | 4 (0.4) | 5 0.5) | 8 (0.7) |
| DVT, Proximal | 9 (1.0) | 20 (2.2) | 8 (0.7) | 14 (1.3) |

**Table 25 Reviewer's summary of pair-wise comparisons and 95% confidence intervals for Main Secondary Endpoint: Major VTE (RECORD 3)**

| Endpoint | Treatment | point estimate [95% CI] using exact method | Point estimate (95% CI ) using Mantel-Haenszel-weighted dfference | P-value |
|---|---|---|---|---|
| PP Population | Rivaroxaban | 1.03%[0.47%, 1.95%] | -1.4 [-2.6%, -0.2] | P=0.025 |
| | Enoxaparin | 2.47% [1.55%, 3.7%] | | |
| | | | | |
| MITT Population | Rivaroxaban | 1.0% [0.5%, 1.9%] | -1.6% [-2.8%, -0.4%] | P=0.01 |
| | Enoxaparin | 2.6% [1.7%, 3.8%] | | |

**Table 26 Reviewer's summary of pair-wise comparisons and 95% confidence intervals for the Main Secondary Endpoint: Major VTE (RECORD 4)**

| Endpoint | Treatment | point estimate [95% CI] using exact method | Point estimate (95% CI ) using Mantel-Haenszel-weighted difference | P-value |
|---|---|---|---|---|
| PP Population | Rivaroxaban | 1.1%[0.54%, 1.9%] | -3.7 [-1.3%, -0.6%] | P=0.456 |
| | Enoxaparin | 1.5% [0.8%, 2.4%] | | |
| | | | | |
| MITT Population | Rivaroxaban | 1.2% [0.6%, 2.0%] | -0.8% [-1.8%, -0.2%] | P=0.124 |
| | Enoxaparin | 2.0% [1.2%, 3.0%] | | |

The following table shows reviewer's summary of secondary efficacy endpoint for DVT, PE and Symptomatic VTE Record 3. Pulmonary embolism and Symptomatic VTE did not show statistically significant between Rivaroxaban group and Enoxpaparin group (Table 27).

**Table 27 Summary of this Secondary Efficacy Endpoint (MITT Population) (RECORD 3)**

| Endpoint | Rivaroxaban N=965 | Enoxaparin N=959 | 95% CI Difference to Enoxaparin |
|---|---|---|---|
| Deep vein thrombosis | 61(6.3) | 86 (9.0) | (-5.0, -0.3) |
| Pulmonary embolism | 5 (0.5) | 8 (0.8) | (-1.2, 0.5) |
| Symptomatic VTE | 11 (1.1) | 18 (1.9) | (-1.93, -0.37) |

The following table shows reviewer's summary of secondary efficacy endpoint for DVT, PE and Symptomatic VTE Record 4. Pulmonary embolism and Symptomatic VTE did not show statistically significant between rivaroxaban group and Enoxapaparin group (Table 28).

**Table 28 Summary of this Secondary efficacy Endpoints (MITT Population) (RECORD 4)**

| Endpoint | Rivaroxaban N=824 | Enoxaparin N=878 | 95% CI Difference to Enoxaparin |
|---|---|---|---|
| Deep vein thrombosis | 79(9.6) | 160 (18.2) | (-5.0, -0.3) |
| Pulmonary embolism | 0 | 4 (0.5) | (-3.16, 0.01) |
| Symptomatic VTE | 8 (1.0) | 24 (2.7) | (-3.16, -0.43) |

## 3.2 Evaluation of Safety

The figures and tables presented below show the observed proportion of subjects with bleeding event using pooled RECORD 1-4 data analyzed over 3 different time periods. Four categories of bleeding that include 1) major bleeding event, 2) major bleeding combined with surgical site bleeding events, 3) major or non-major clinically relevant bleeding event and 4) any bleeding event are presented. Tables include hazard ratio and the corresponding 95% confidence interval for

time to first event. The p-value using Cox-regression model for time to first event and p-value with time to multiple events using Andersen-Gill (AG) proportional hazards model can also be found in the tables (Table 29).

**Bleeding Event for Total Duration**

A statistically significant increase was observed in the proportion of subjects with bleeding event over the total duration for major bleeding event (24 (0.39%) vs 13 (0.21%)), major bleeding combined with surgical site bleeding events (111 (1.8%) vs 85 (1.37%)), and major or non-major clinically relevant bleeding event (197 (3.19%) vs 158 (2.55%)) in Rivaroxaban group compared to active control (Enoxaparin) group. The hazard ratios are all > 1 by using Cox Propotional Hazard model in Rivaroxaban compared with Enoxaparin, and p-values for major bleeding, for major bleeding combined with surgical site and for major or non-major clinically relevant bleeding event are all statistically significant at 10% level of significance in favor of Enoxaparin. The conclusions stay unchanged whether or not time to first event or time to multiple events is considered.

**Figure 2 Percentage of Bleeding Event Total duration in Pooled Study**

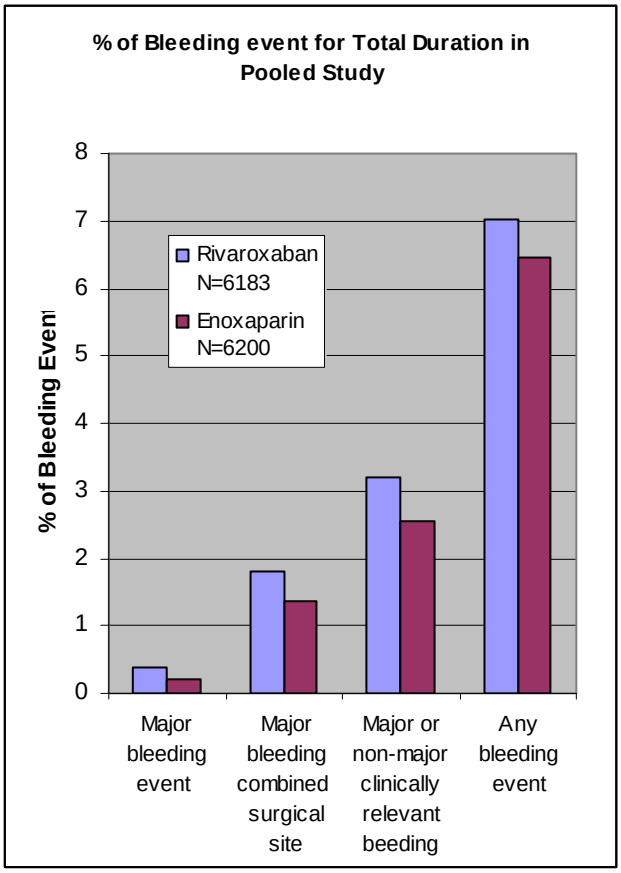


**Table 29 Percentage of Bleeding Event Total duration in Pooled Study**

| Endpoint | Rivaroxaban N=6183 | Enoxaparin N=6200 | Hazard Ratio for time to first event (95% CI) | P-value (time to first event) | P-value (time to multiple event |
|---|---|---|---|---|---|
| Major bleeding | 24 (0.39%) | 13 (0.21%) | 1.8 (0.9, 3.6) | 0.076 | 0.05 |
| Major bleeding combined with surgical site | 111 (1.80%) | 85 (1.37%) | 1.3 (1.0, 1.7) | 0.06 | 0.05 |
| Major or non-major clinically relevant bleeding | 197 (3.19%) | 158 (2.55%) | 1.3 (1, 1.5) | 0.039 | 0.02 |
| Any bleeding | 434 (7.02%) | 401 (6.47) | 1.1 (0.9, 1.2) | 0.3 | 0.3 |

**Bleeding Event until Day 12±2**

Analysis of the data until day 12±2 again showed that significant increase was observed in the proportion of subjects with bleeding event for major bleeding event (21 (0.34%) vs 13 (0.21%)), major bleeding combined with surgical site bleeding events (111 (1.8%) vs 84 (1.35%) ), major or non-major clinically relevant bleeding event (176 (2.85%) vs 152 (2.45%) ) and any bleeding event (409 (6.61%) vs 384 (6.19)) in Rivaroxaban group compared to Enoxaparin control group. The hazard ratios are all > 1 by using Cox Proportional Hazard model, and p-values for major bleeding combined with surgical site bleeding event are 0.08 and 0.06 (statistically significant at 10% level) for time to first event and time to multiple events, respectively (Table 30). The conclusions stay unchanged whether or not time to first event or time to multiple events is considered

**Figure 3 Percentage of Bleeding Event until Day 12 ± 2 in Pooled Study**

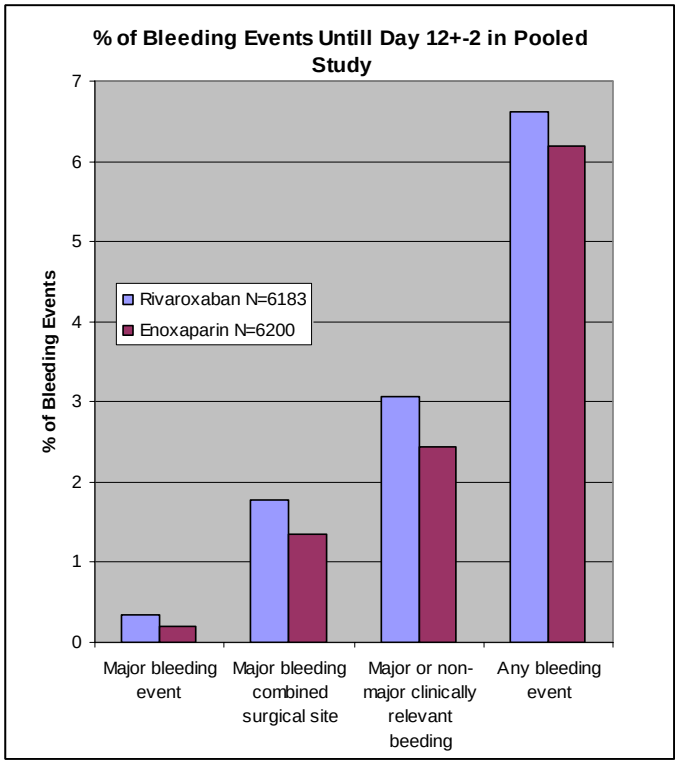



**Table 30 Percentage of Bleeding Event until Day 12 ± 2 in Pooled Study**

| Endpoint | Rivaroxaban N=6183 | Enoxaparin N=6200 | Hazard Ratio for time to first event (95% CI) | P-value (time to first event) | P-value (time to multiple event |
|---|---|---|---|---|---|
| Major bleeding | 21 (0.34%) | 13 (0.21%) | 1.61 (0.8, 3.2) | 0.175 | 0.09 |
| Major bleeding combined with surgical site | 108 (1.75%) | 84 (1.35%) | 1.3 (1.0, 1.7) | 0.082 | 0.06 |
| Major or non-major clinically relevant bleeding | 176 (2.85%) | 152 (2.45%) | 1.2 (0.9, 0.4) | 0.186 | 0.17 |
| Any bleeding | 409 (6.61%) | 384 (6.19) | 1.1 (0.9, 1.2) | 0.38 | 0.3 |

**Bleeding Event for Active Control Phase**

When data were analyzed over active control phase, again a statistically significant increase was observed in the proportion of subjects with bleeding event for major bleeding event (23 (0.37%) vs 13 (0.21%)), major bleeding combined with surgical site bleeding events (110 (1.78%) vs 84 (1.35%)), and major or non-major clinically relevant bleeding event (190 (3.07%) vs 156 (2.52%) in Rivaroxaban group compared to active control (Enoxaparin) group. The hazard ratios are all > 1 by using Cox Proportional Hazard model, and p-values for major bleeding, major bleeding combined with surgical site and for major or non-major clinically relevant bleeding event are all statistically significant at 10% level of significance in favor of Enoxaparin and against Rivaroxaban for both time to first event and time to multiple events (Table 31). The conclusions stay unchanged whether or not time to first event or time to multiple events is considered

**Figure 4 Percentage of Bleeding Event for Active Control Phase in Pooled Study**

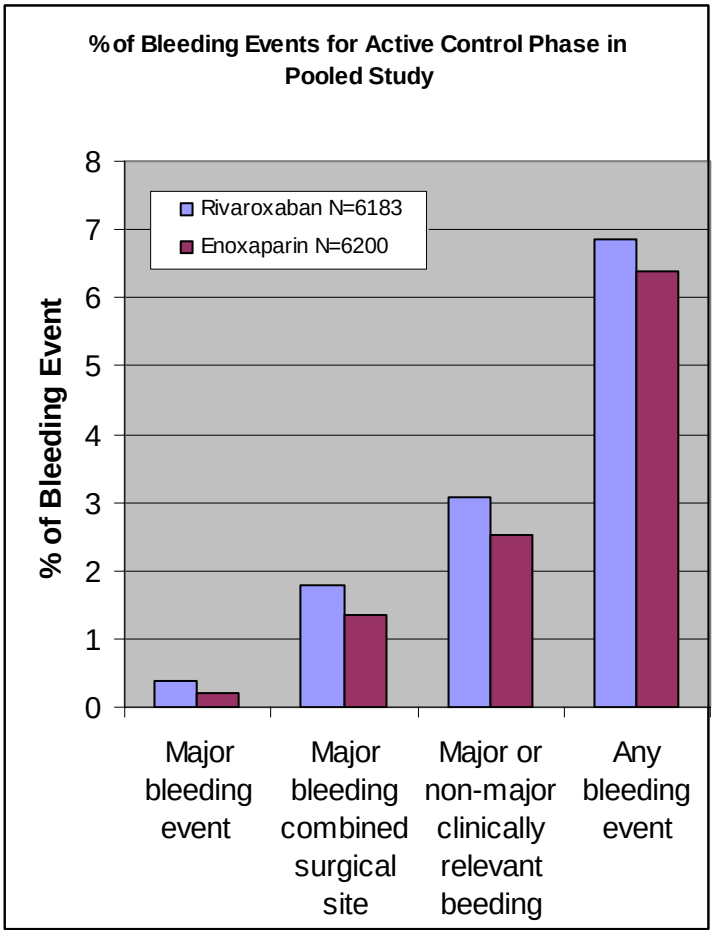


**Table 31 Percentage of Bleeding Event for Active Control Phase in Pooled Study**

| Endpoint | Rivaroxaban N=6183 | Enoxaparin N=6200 | Hazard Ratio for time to first event (95% CI) | P-value (time to first event) | P-value (time to multiple event |
|---|---|---|---|---|---|
| Major bleeding | 23 (0.37%) | 13 (0.21%) | 1.8 (0.9, 3.5) | 0.1 | 0.08 |
| Major bleeding combined with surgical site | 110 (1.78%) | 84 (1.35%) | 1.3 (1.0, 1.7) | 0.06 | 0.049 |
| Major or non-major clinically relevant bleeding | 190 (3.07%) | 156 (2.52%) | 1.3 (1, 1.5) | 0.068 | 0.055 |
| Any bleeding | 424 (6.86%) | 397(6.40 %) | 1.1 (0.9, 1.2) | 0.3 | 0.19 |

**Conclusion for Bleeding Analyses**

The data provided in this NDA demonstrate that for patients following THR and TKR surgery, administration of Rivaroxaban for prophylaxis of DVT and PE increases the incidence of bleeding in comparison with the active control Enoxaparin, based on the results from categories of major bleeding alone or combined with surgical site or non-major clinically relevant bleeding as assessed by the Bleeding Event Adjudication Committee (AC/BE). It is known (from the label) that the most common side effect associated with using Enoxaparin is the risk of bleeding. The evidence that administration of Rivaroxaban could increase bleeding events relative to Enoxaparin amplifies this safety concern for Rivaroxaban in comparison to placebo in the setting of prophylaxis of DVT and PE following THR or TKR surgery.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 GENDER, RACE AND AGE

#### 4.1.1 Subgroup Analysis for RECORD 1

Table 32 shows the reviewer's summary of incidence rates of primary efficacy endpoint and 95% confidence interval of difference using exact methods stratified by baseline covariates for MITT population. In general, a treatment difference in favor of Rivaroxaban was observed in each of the subgroups that had sample size of at least 10% of the entire population. The results for age indicated a trend toward a greater incidence rate of the primary efficacy variable in older subjects. There is no between group difference for the patient whose age greater than 75 years (95% CI: -5.87%, 3.78). The surgeries of longer duration showed a trend towards higher incidence rates. There is no statistical difference between two groups for the patient whose duration of surgery ≥ 2 hours.

**Table 32 Summary of Incidence Rates of Primary Efficacy Endpoint Stratified by Baseline Covariates for MITT Population (RECORD 1)**

| Baseline Covariate | | Rivaroxaban (N=1,595) n/N (%) | Enoxaparin (N=1,558) n/N (%) | 95% CI of difference using exact methods |
|---|---|---|---|---|
| Gender | Male | 9/745 (1.21%) | 24/710 (3.38%) | [-3.88%, -0.56%] |
| | Female | 9/850 (1.06%) | 34/848 (4.01%) | [-4.58%,-1.37%] |
| Age | <65 years | 4/848 (0.47%) | 23/797 (2.89%) | [-3.85%, -1.15%] |
| | 65-75 years | 7/579 (1.21%) | 25/569 (4.39%) | [-5.31%, -1.09%] |
| | >75 years | 7/168 (4.17%) | 10/192 (5.21%) | [-5.87%, 3.76%] |
| Any VTE Risk Factor | No | 18/1482 (1.21%) | 51/1427 (3.57%) | [-3.54%, -1.26%] |
| | Yes | 0/32 | 7/131 (5.34%) | [-10.70%, -1.60%] |
| History of VTE | No | 18/1563 (1.15%) | 54/1525 (3.54%) | [-3.53%, -1.31%] |
| | Yes | 0/32 | 4/33 (12.1%) | [-28.20,-0.44] |
| Race | Missing | 2/74 (2.70%) | 3/73 (4.11%) | [-9.08%, 5.81%] |
| | White | 16/1491 (1.07%) | 54/1452 (3.72%) | [-3.83%, -1.55%] |
| | Black | 0/11 | 0/13 | [-25.84%, 28.49%] |
| | Asian | 0/2 | 0/2 | [-84.19%, 84.16%] |
| | American Indian | 0/1 | | |
| | Hispanic | 0/12 | 0/11 | [-28.49%, 26.46%] |
| Duration of Surgery | < 2H | 12/1348 (0.89%) | 43/1289 (3.34%) | [-3.64%, -1.34%] |
| | >=2H | 6/246 (2.44%) | 15/267 (5.62%) | [-6.92%, 0.33%] |

Table 33 shows exploratory logistic regression with a stepwise variable selection process of the baseline covariates using an entry significance lever of 5%. The treatment group was included in the model as fixed term. Age and duration of surgery were selected as statistically significant for

MITT population (p=0.003). This result indicates that age and duration of surgery have an influence on VTE events. The odds ratio of the treatment effect after adding baseline covariates is still 0.302 (p<0.0001, 95% CI [0.177, 0.516]).

**Table 33 Logistic Regression Analysis of the Primary Efficacy Endpoint (RECORD 1)**

| Explanatory variables | P-value | Comparison the odds ratio is estimated for | Odds ratio | 95% CI |
|---|---|---|---|---|
| Treatment group | <0.0001 | Rivaroxaban vs Enoxaparin | 0.302 | [0.177, 0.516] |
| Age | 0.003 | <65 yrs vs >75 yrs | 0.34 | [0.182, 0.634] |
| | | 65-75 yrs. Vs >75 yrs | 0.595 | [0.325, 1.091] |
| Duration of surgery | 0.0108 | <2H vs >= 2H | 0.492 | [0.294, 0.826] |

### 4.1.2 Subgroup Analysis for RECORD 2

The following table shows the reviewer's summary of incidence rates of primary efficacy endpoint and 95% confidence interval of difference using exact methods stratified by baseline covariates for MITT population (Table 34). In general, a treatment difference in favor of Rivaroxaban 10 mg od was observed in each of the subgroups that had sample size of at least 10% of the entire population. The results for age indicated a trend toward a greater incidence rate of the primary efficacy variable in older subjects. The impact of the history of VTE can not be assessed, as there are only 22 subjects in the MITT population.

**Table 34 Summary of Incidence Rates of Primary Efficacy Endpoint Stratified by Baseline Covariates for MITT Population (RECORD 2)**

| Baseline Covariate | | Rivaroxaban (N=1595) n/N (%) | Enoxaparin (N=1558) n/N (%) | 95% CI of difference using exact methods |
|---|---|---|---|---|
| Gender | Male | 1/409 (1.21%) | 33/425 (7.95%) | [-10.72%, -5.27%] |
| | Female | 16/455 (3.52%) | 48/454 (4.01%) | [-10.53%,-3.71%] |
| Age | <65 years | 4/470 (0.85%) | 28/480 (5.89%) | [-7.52%, -2.73%] |
| | 65-75 years | 8/302 (2.65%) | 35/285 (12.28%) | [-14.18%, -5.21%] |
| | >75 years | 5/92 (4.17%) | 18/19(5.21%) | [-21.21%, -2.83%] |
| Any VTE Risk Factor | No | 14/835 (1.68%) | 75/830 (9.04%) | [-9.62%, -5.24%] |
| | Yes | 3/29 (10.34) | 6/39 (15.38%) | [-22.01%, 13.66%] |
| History of VTE | No | 17/858 (1.98%) | 78/853 (9.04%) | [-9.62%, -5.24%] |
| | Yes | 0/6 | 3/16 (12.1%) | [-46.09%,28.04%] |
| Duration of Surgery | < 2H | 12/1348 (0.89%) | 43/1289 (3.34%) | [-3.64%, -1.34%] |
| | >=2H | 8/258 (3.10%) | 26/260 (10%) | [-11.49%, -2.11%] |

The following table shows exploratory logistic regression with a stepwise variable selection process of the baseline covariates using an entry significance lever of 5% (Table 35). The treatment group was included in the model as fixed term. Age and VTE Risk Factors were selected as statistically significant for MITT population.This result indicates that age and VTE Risk Factors have an influence on VTE events.

**Table 35 Logistic regression analysis of the primary efficacy endpoint for MITT population (RECORD 2)**

| Explanatory variables | P-value | Comparison the odds ratio is estimated for | Odds ratio | 95% CI |
|---|---|---|---|---|
| Treatment group | <0.0001 | Rivaroxaban vs Enoxaparin | 0.151 | [0.079, 0.250] |
| Age | 0.0009 | <65 yrs vs >75 yrs | 0.317 | [0.156, 0.642] |
| | | 65-75 yrs. Vs >75 yrs | 0.742 | [0.377, 1.463] |
| VTE Risk Factors (No/Yes) | 0.0035 | No vs Yes | 0.245 | [0.105, 0.571] |

### 4.1.3 Subgroup Analysis for RECORD 3and RECORD 4

The reviewer's findings for the RECORD 3 and RECORD 4 studies were similar to those in RECORD 1 and RECORD 2.

## 4.2 OTHER SPECIAL/SUBGOUP POPULATIONS

There were no special populations studied or special subgroups examined in this submission.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

#### 5.1.1 Integrated Analyses of Bleeding

Please see section 3.2

#### 5.1.2 Integrated Analyses for Assessment of Symptomatic VTE

Of particular note were the pre-specified integrated analyses for the RECORD studies. It was clearly stated in the Applicant's statistical analysis plan that these analyses were to be performed as exploratory and not for confirmatory hypothesis-testing. The primary endpoint in these analyses was a comparison of the rates of symptomatic VTE (DVT and/or PE) or death from all causes (which ever comes first) during the treatment period of the studies. The endpoint was analyzed as a time to event comparison using a Cox regression model with study (RECORD 1, 2, 3 and 4) and treatment group as covariates to determine the hazard ratios for the primary endpoint and the corresponding 95% CI. The analytical population consisted of all patients who received at least one dose of study drug (the "safety population").

A summary of the rates of symptomatic VTE or death during the treatment phase of each of the RECORD studies is shown in the following table (Table 36).

**Table 36. "Symptomatic VTE or Death" in RECORD Studies (safety population)**

| Out-come | RECORD 1 (hip) | | RECORD 2 (hip) | | RECORD 3 (knee) | | RECORD 4 (knee) | |
|---|---|---|---|---|---|---|---|---|
| | Riva n = 2209 | Enox n = 2224 | Riva n = 1228 | Enox n = 1229 | Riva n = 1220 | Enox n = 1239 | Riva n = 1526 | Enox n = 1508 |
| Any event | 10 (0.5%) | 15 (0.7%) | 5 (0.4%) | 20 (1.6%) | 8 (0.7%) | 26 (2.1%) | 12 (0.8%) | 21 (1.4%) |
| *Components of "Symptomatic VTE or Death" Endpoint** | | | | | | | | |
| DVT | 3 (0.1%) | 9 (0.4%) | 2 (0.2%) | 10 (0.8%) | 8 (0.7%) | 20 (1.6%) | 6 (0.4%) | 10 (0.7%) |
| PE | 4 (0.2%) | 2 (0.1%) | 1 (0.1%) | 5 (0.4%) | 0 | 4 (0.3%) | 5 (0.3%) | 8 (0.5%) |
| Death | 4 (0.2%) | 5 (0.2%) | 2 (0.2%) | 3(+3)^ (0.5%) | 0 | 2 (0.2%) | 2 (0.1%) | 3 (0.2%) |

*some patients could have both a PE and DVT
^ 3 of 6 deaths occurred during the placebo treatment period

The Sponsor's integrated summary (all 4 studies combined) is shown in Table 37.

**Table 37. Sponsor's Integrated Summary of "Symptomatic VTE or Death" in RECORD Studies (safety population; active treatment period)**

| Outcome | Rivaroxaban n = 6183 | Enoxaparin n = 6200 | Hazard Ratio, point estimate and 95% CI | p-value |
|---|---|---|---|---|
| VTE/Death | 35 (0.6%) | 82 (1.3%) | 0.42 (0.29 - 0.63) | < 0.05 |
| VTE (DVT &/or PE) | 28 (0.5%) | 68 (1.1%) | 0.41 (0.26 - 0.64) | < 0.05 |
| PE | 10 (0.2%) | 19 (0.3%) | 0.53 (0.24 - 1.13) | 0.10 |
| Death | 8 (0.1%) | 13(+3)^ (0.3%) | 0.50 (0.21 - 1.17) | 0.11 |

^ 3 of the deaths occurred during the placebo treatment period in RECORD 2 study

Although, it appears that twice as many deaths were reported in the Enoxaparin group as in the Rivaroxaban group, it must be noted that 5 of the 8 excess deaths attributed to the Enoxaparin group either occurred during the placebo-controlled period of RECORD 2 study or occurred in the RECORD 3 study with lower Enoxaparin dose. Overall, the numbers of death were too small to show a nominal statistically significant difference between the two groups. Determining the cause of death is vulnerable to considerable error. Nevertheless, the investigators assessed pulmonary emboli as the cause for death in thee patients in the Rivaroxaban group and the cause of death in two Enoxaparin group patients.

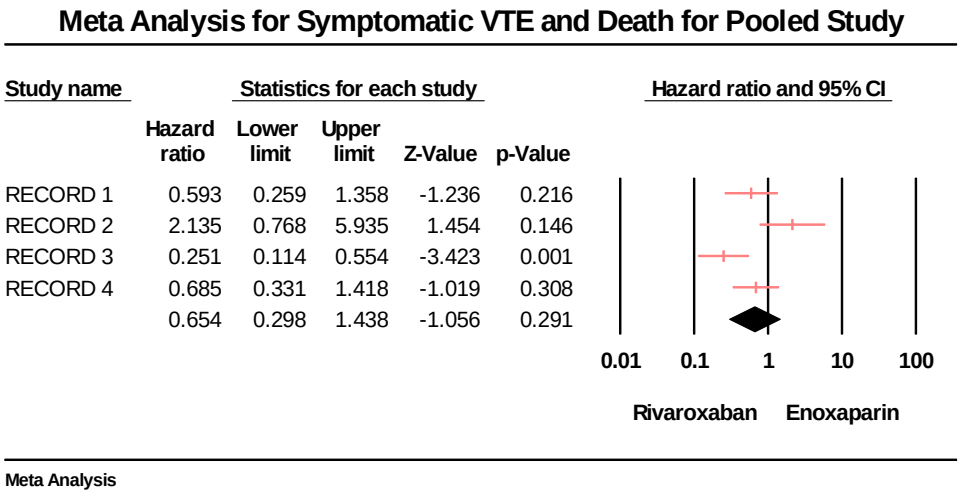
Statistical review of integrated analyses suggests that the sponsor's pre-specified statistical analysis plan for the pooled analyses was that of the exploratory nature with no adjustments to the significance levels to account for multiple comparisons on the same data or for multiple efficacy variables. Another issue is that of pool-ability of the data from all 4 RECORD studies. As noted before, RECORD 2 study used shorter duration of Enoxaparin and RECORD 3 study used lower (unapproved) dose of Enoxaparin. Therefore simple pooling of data from all four studies without any adjustment may lead to biased comparison with underestimated effect of Enoxaparin. Statistical reviewer conducted several sensitivity analyses to address this issue. The goal of all these analyses was to examine exploratory evidence of potential (to be tested in another confirmatory study) superiority of Rivaroxaban over Enoxaparin for reduction in "Symptomatic VTE or Death". These analyses including the sponsor's analysis are not intended for confirmatory statistical inference.

For pooled data, the sponsor's combined all 4 studies without weighting and analysis was performed as if the data were derived from a single sample. Under this plan, important study characteristics such as type of surgery, dose, and duration were ignored. Analysis based on simple pooling using Cox regression without adjusting any covariates showed hazard ratio is 0.4, and 95% confidence interval is (0.29, 0.63), P-value<0.001 .

This reviewer conducted pooled analyses of the data from 4 RECORD studies using meta-analysis and proportional hazard with adjustments for clinically relevant covariates model. Meta

analysis provides ability to control between-study variation and this is important given that background or control rates could be different from study to study. Proportional hazard model with adjustments for clinically relevant covariates could reduce model bias and increase model power. The meta-analysis showed the overall hazard ratio is 0.654, and the overall P-value is 0.291. This demonstrate that there is no statistically significant difference between Rivaroxaban group and Enoxaparin groups (Figure 5)

**Figure 5 Meta- Analysis for Symptomatic VTE and Death for Pooled Study**




The Proportional Hazard regression model with adjustments for study, treatment duration and age showed that hazard ratio is 0.69, 95% confidence interval is (0.46, 1.04), and P-value is 0.07 which is consistent with the result from meta-analysis that the difference between Rivaroxaban group and Enoxaparin group in terms of Symptomatic VTE or death is not statistically significant.

These analyses may be subject to criticism due to the fact that in RECORD 2 study treatment and treatment duration are correlated and using both these variables in the model may lead to problems of co-linearity and unstable parameter estimates in that study. However these concerns are reduced when the data from all 4 studies are combined. One could also argue that the confounding of treatment and treatment duration in RECORD 2 study renders this study not suitable by virtue of the study design to assess the treatment effect. In addition, one could argue

that RECORD 3 study used a lower unapproved dose of Enoxaparin and should not be pooled with the other studies and thus one is left with just RECORD 1 and RECORD 4 studies for pooled integrated analyses. Statistical reviewer conducted this and several additional sensitivity analyses. The following table presents results from those analyses. As one can see, the nominal p-values in all these sensitivity analyses exceed 0.05 with upper limits of the confidence intervals for hazard ratio exceeding 1.

**Table 38.FDA Integrated Summary of "Symptomatic VTE or Death" in RECORD Studies (safety population; active treatment period)**

| Analysis | Hazard Ratio | 95% CI | p-value |
|---|---|---|---|
| Pooled 1, 4 (no adjustments) | 0.61 | (0.36, 1.03) | 0.07 |
| Pooled 1, 4 (adjusted for treatdur, study) | 0.67 | (0.39, 1.15) | 0.14 |
| Meta Analysis of 1, 4 (adjusted for treatdur, study) | 0.61 | (0.36, 1.04) | 0.07 |
| Pooled 1,2,3,4 (adjusted for treatdur, study, age) | 0.69 | (0.46, 1.04) | 0.07 |
| Meta analysis of 1,2,3,4 (adjusted for treatdur, study, age) | 0.65 | (0.30, 1.44) | 0.29 |

### 5.1.3 Statistical Issues

1. There are some issues and findings in the bleeding analyses.

   Sponsor used Cox model for time to first event for bleeding analyses, although bleeding events are time dependent with multiple observations per subject and it is more appropriate to use time-to-event data in the multiple event setting. In this review, the Andersen-Gill (AG) formulation of the proportional hazards model as a counting process is used for the assessment of benefit in terms of bleeding. The results from these analyses are given in Section 3.2 and demonstrate that for patients following THR and TKR surgery, administration of Rivaroxaban for prophylaxis of DVT and PE increases the incidence of bleeding in comparison with the active control Enoxaparin, based on the results from categories of major bleeding alone or combined with surgical site or non-major clinically relevant bleeding as assessed by the Bleeding Event Adjudication Committee (AC/BE). It is known (from the label) that the most common side effect associated with using Enoxaparin is the risk of bleeding. The evidence that administration of Rivaroxaban could lead to bleeding events in significantly more patients relative to Enoxaparin amplifies this safety concern for Rivaroxaban in comparison to placebo in the setting of prophylaxis of DVT and PE following THR or TKR surgery.

2. Two of the four phase III RECORD studies were not appropriate for the US clinical use of the comparator drug Enoxaparin. RECORD 3 trial used a lower regimen not approved for Enoxaparin in US for TKR, whereas RECORD 2 used shorter duration of treatment in Enoxaparin group. Data from these trials are likely to have resulted in underestimation of Enoxaparin's treatment effect.

3. All RECORD study protocols included several secondary efficacy endpoints. However the study statistical analysis plans or SAPs did not include strong control of Type I error rate for confirmatory evidence of benefit based on secondary endpoints. A clinically important endpoint in these patient populations is Symptomatic VTE or Death. However nominal p-values for this secondary endpoints were <0.05 only for RECORD 2 and RECORD 3 studies which used shorter duration of treatment in RECORD 2 and used unapproved lower Enoxaparin regimen in RECORD 3 study. Data from these trials are likely to have resulted in underestimation of Enoxaparin's benefit in terms of Symptomatic VTE or death (Table 39).

**Table 39 Results for Symptomatic VTE or Death by individual study**

| RECORD | Rivaroxaban | Enoxaparin | Hazard Ratio (95% CI) |
|---|---|---|---|
| 1 | 10/2209<br>0.45% | 15/2224<br>0.67% | 0.7<br>(0.3, 1.5) |
| 2 | 5/1228<br>0.41% | 20/1229<br>1.6% | 0.2<br>(0.1, 0.7) |
| 3 | 8/1220<br>0.66% | 26/1239<br>2.1% | 0.3<br>(0.1, 0.7) |
| 4 | 12/1526<br>0.79 | 21/1508<br>1.4% | 0.6<br>(0.3, 1.2) |

Analysis results of major secondary endpoint for Pulmonary Thrombosis showed that in all four pivotal studies, the difference between Rivaroxaban group and Enoxaparin group was not statistically significant at 5% nominal level of significance. (Table 41).

**Table 40 P-value using fisher exact method for comparison of Rivaroxaban to Enoxaparin for PE.**

| Study | Pulmonary Thrombosis |
|---|---|
| RECORD 1 | P=0.69 |
| RECORD 2 | P=0.06 |
| RECORD 3 | P=0.12 |
| RECORD 4 | P=0.42 |

4. The sponsor analyzed these data from all 4 RECORD studies in an integrated analysis. When then statistical analysis plan for the integrated analysis was finalized to include all 4 record studies, the results from integrated data from record 1, 2 and 3 were known. This is departure from pre-specification. Pooled exploratory analyses of these data are addressed in Section 5.1 in detail.

5. Baseline imbalances between the treatment groups were observed with respect to age, duration of surgery and current alcohol consumption in RECORD 1 study. Age and duration of surgery were reported to be risk factors for the primary efficacy variable and were identified as having a statistically significant effect by the exploratory logistic regression analysis. This result indicates that age and duration of surgery have an influence on VTE event. In RECORD 2, age and VTE risk levels were reported to be risk factors for the primary efficacy variable and there were identified as having a statistically significant effect by the exploratory logistic regression analysis. This result indicates that age and VTE risk levels have an influence on VTE event in RECORD 1 and RECORD 2 study.

6. Baseline imbalances between the two treatments were also observed with respect to gender and thromboemblism risk factors in RECORD 3 study. Both of these were associated with a greater incidence of the primary efficacy variable in this study and there were a greater number of females and subjects with thromboembolism risk factors in the Rivaroxaban group as compared to the Enoxaparin. Exploratory logistic regression analyses were performed to assess the effect of baseline covariates. For the primary efficacy variable, none of the baseline covariates were identified as being statistically significant.

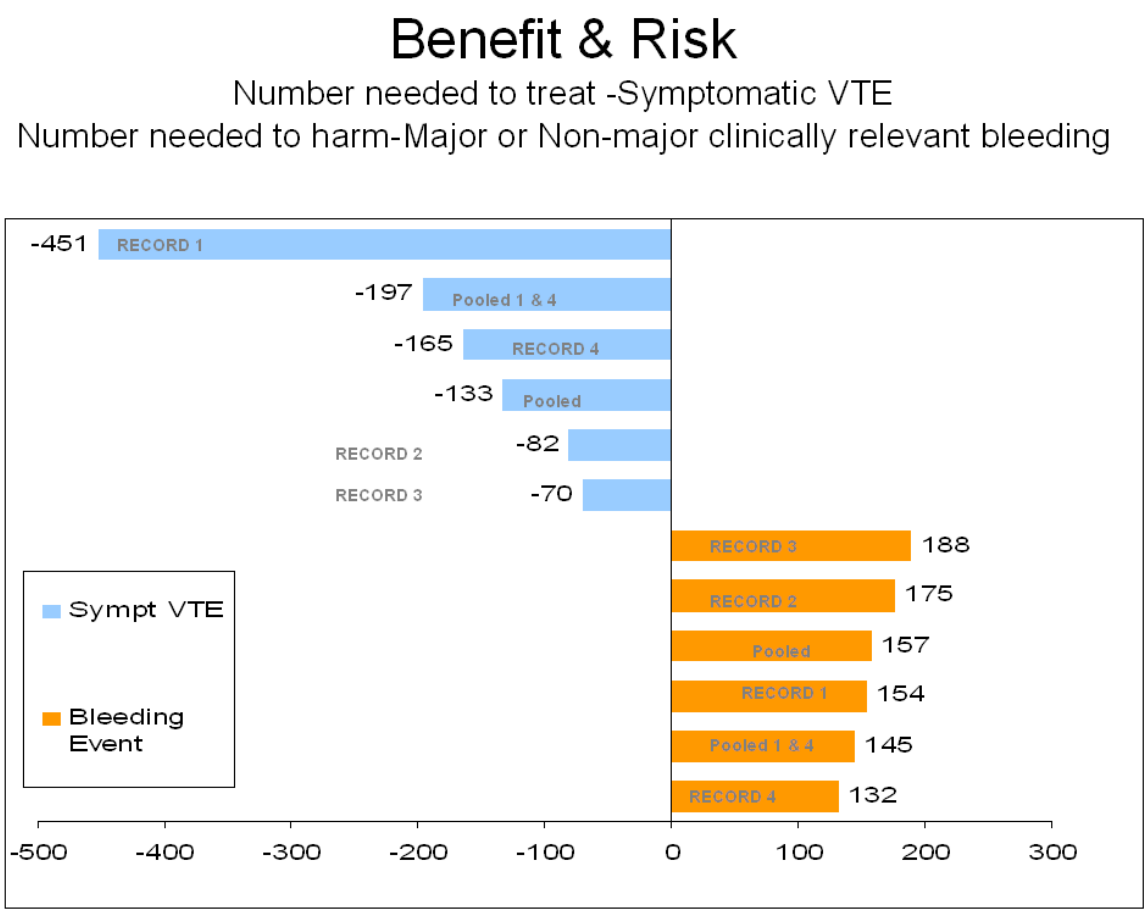
7. For the method of Mantel-Haenszel-weighted differences in proportions for the primary efficacy analysis, p-values were derived as the smallest significance level at which the hypothesis would be rejected for the given observation. As a consequence, the p-values might differ from those which would have resulted from applying Mantel-Haenszel test with no difference in proportion. This is due to the fact that for the calculation of the CI the estimated standard error is based on observed rates and not the hypothesized rates. In RECORD studies, the results are consistent between these methods.

8. In RECORD 4 Study, the MITT validity rate of 61% was lower than anticipated, although the rates were similar in the two treatment groups. Logistic regression analysis was performed, mainly to assess the effect of baseline covariates on the primary efficacy variable. Geographic region was selected as statistically significant. This result indicates that geographic region has an influence on VTE events.

9. The following figure (Figure 6) shows the results from benefit and risk assessment. Negative 451 from RECORD 1 study means that about one in every 451 patients will benefit from the Rivaroxaban group compared to the Enoxaparin group for RECORD 1 study. So RECORD 1 shows least benefit by using Rivaroxaban versus Enoxaparin. In contrast, negative 70 means that about one in every 70 patients will benefit from Rivaroxaban treatment compared to Enoxaparin. So RECORD 3 shows the most benefit of using Rivaroxaban.

However, RECORD 3 study used unapproved lower Enoxaparin dose regimen. This result is consistent with the result from efficacy analysis. For the bleeding side effect, 132 means that about one in every 132 patients will be harmed by Rivaroxaban group relative to Enoxaparin for RECORD 4 study, and so on.

**Figure 6 Results for Benefit and Risk Assessment**




## 5.2 Conclusions and Recommendations

Four Phase III pivotal clinical studies were included in this New Drug Application (NDA) submission. Statistical analysis results, based on the data of the 4 pivotal studies, demonstrate the drug efficacy using Rivaroxaban in the treatment of major VTE when compared with Enoxaparin control. Findings from using different approaches to deal with missing data issues with the primary endpoint consistently concluded the robustness of the primary efficacy results.

However, the primary efficacy endpoint was the incidence of total VTE that defined as the composite of any DVT, non-fatal PE, or all cause death. Among the 3 components of the composite endpoint, only incidence of DVT in Rivaroxaban group was significantly lower than that in active-control group. In all four pivotal studies, incidences of PE and all cause death were rare. No conclusions can be drawn regarding treatment effect of Rivaroxaban on PE and all cause death, when compared to Enoxaparin control. It is suggested to include this fact in labeling if approval is granted.

All RECORD study protocols included several secondary efficacy endpoints. However, the study statistical analysis plans or SAPs did not include strong control Type I error rate for confirmatory evidence of benefit based on secondary endpoints. A clinically important endpoint in these patient populations is Symptomatic VTE or Death. However Nominal p-values for this secondary endpoints were <0.05 only for RECORD 2 and RECORD 3 studies which used shorter duration of treatment in RECORD 2 and used unapproved lower Enoxaparin regimen in RECORD 3 study. Data from these trials are likely to have resulted in underestimation of Enoxaparin's benefit in terms of Symptomatic VTE. The pooled analysis from this reviewer shows that Rivaroxaban does not have statistically significant difference for Symptomatic VTE compared to Enoxaparin. From the bleeding analysis result, it demonstrated that Rivaroxaban increases the bleeding event compared to Enoxaparin. These issues should be addressed in labeling.

**SIGNATURES/DISTRIBUTION LIST (Optional)**

An example of this optional documentation is as follows:

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Date: 5/2/09

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Statistical Team Leader: Jyoti Zalkikar

Biometrics Division Director: Aloka Chakravarty

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HFD-160/Project Manager: Marcus Cato
HFD-160/Medical Officer: Min Lu
HFD-160/Medical Team Leader: Kathy Robie Suh
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## Clinical Studies

| | |
|---|---|
| **NDA/Serial Number:** | 22-406; |
| **Drug Name:** | Xarelto (Rivaroxaban) |
| **Dosages:** | 10 mg QD tablet |
| **Indication(s):** | Prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery |
| **Applicant:** | Johnson and Johnson |
| **Date(s):** | Submission Date: July 28, 2008 |
| | PDUFA Goal Date: May 28, 2009 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | Quantitative Safety and Pharmacoepidemiology Division (DB-VII) |
| **Statistical Reviewer:** | Chava Zibman, PhD |
| **Concurring Reviewers:** | Antonio Paredes, MA, MS |
| | George Rochester, PhD |
| **Medical Division:** | Division of Medical Imaging and Hematology Products |
| **Clinical Team:** | Kathy Robie-Suh, MD, PhD (Team Leader); |
| | Min Lu, MD (Medical Officer) |
| **Project Manager:** | Diane Leaman, RPM; Marcus Cato, MBA |

**Keywords:** Hepatotoxicity, FDA DILI Guidance, Hy's Law, Anti-coagulant, Deep Vein Thrombosis, Pulmonary Embolism, Total Hip Replacement, Total Knee Replacement

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

This memorandum summarizes the results of a safety evaluation of four randomized phase 3 clinical trials evaluating the efficacy and safety of Rivaroxaban. Subjects were randomly allocated to either Rivaroxaban or Enoxaparin (the active control) and assessed for liver toxicity via liver assessment tests conducted at specified time points during the studies. This safety evaluation is based on the results from the liver assessment tests as well as on reports of hepatobiliary adverse events. This assessment is based on data aggregated over all four studies. The safety population of these studies consisted of 6183 adult patients receiving Rivaroxaban and 6200 receiving Enoxaparin as a prophylaxis for Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) following total hip or total knee replacement surgery.

Because of the structure of the data and issues associated with data quality, no formal statistical inference was conducted in the following analysis. Instead, this evaluation of the submitted data consists in summarizing the liver assessment test results and frequencies of hepatobiliary adverse events in the data.

A larger proportion of Rivaraxoban patients (74.2% versus 63%) than Enoxaparin patients have post-baseline ALT levels that remain below the upper limit of normal (ULN) following treatment. They have peak TBL levels below the ULN (93.1% versus 93.5%) in comparable proportions. In addition, a larger proportion (75.5% versus 65.4%) of patients receiving Rivaraxoban maintain normal levels of aspartate aminotransferase (AST). A slightly larger proportion of Rivaraxoban patients than Enoxaparin patients had normal peak levels of alkaline phosphatase (96.1% and 94.7%).

Of those patients with peak post-baseline ALT above three times the ULN, 9 out of 123 (7.3% ) in the Rivaroxaban group and 13 out of 201 (6.5%) in the Enoxaparin group had ALT levels above that threshold pre-baseline as well. Similarly, 4 out of 21 (19.0%) of Rivaroxaban patients and 2 out of 31 (6.5%) of Enoxaparin patients with peak post-baseline TBL levels above twice the ULN also had pre-baseline levels in that range.

Patients with both peak ALT levels at least 3 time the ULN and peak TBL levels at least twice the ULN at any time post-baseline meet two of the criteria of Hy's Law, as per FDA’s guidance. Hy's Law patients are believed to be at heightened risk of liver failure. Ten patients in each treatment group (approximately 0.2% of each group) have peak ALT and TBL levels in the Hy's Law range. Five of these (3 Rivaroxaban, 2 Enoxaparin), however, meet one or both of these initial criteria prior to receiving the treatment drug. Five more (3 Rivaroxaban, 2 Enoxaparin) have peak ALP levels above twice the ULN (which is inconsistent with the Hy’s Law criteria). We do not find an excess number of potential Hy’s Law cases among the Rivaraxoban patients as compared to those receiving Enoxaparin.

There were 35 adverse events reported in 28 Rivaraxoban patients in the “Hepatobiliary Disorders” system organ class (SOC) of the MedDRA classification system. Eight of these were

serious. In the Enoxaparin group, 39 patients had reports of 45 hepatobiliary events, 9 of which were serious.

In summary, according to the data evaluated in this memorandum, it might be difficult to differentiate between Rivaroxaban and Enoxaparin patients based on signals of liver toxicity in the data. In fact, a smaller proportion of Rivaroxaban patients than Enoxaparin patients have elevated enzyme or TBL levels or experience hepatobiliary adverse events.

### 1.2 Brief Overview of Clinical Studies

This review evaluates the data from four Phase 3 double-blinded randomized clinical trials (labeled as RECORD 1, RECORD 2, RECORD 3, and RECORD 4) intended to evaluate Rivaroxaban as a prophylaxis for Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) following total hip or total knee replacement surgery. RECORD 1 (4541 patients) and RECORD 2 (2509 patients) were concerned with hip replacement patients, while RECORD 3 (2531 patients) and RECORD 4 (3148 patients) were concerned with knee replacement patients. The treatment periods for these studies were of 12 or 35 days with a one-month follow-up period for all. Note that additional studies associated with this application were, or are expected to be, submitted; however, since the original NDA was based on results from the above four studies, this analysis focuses solely on the 12,383 patients (Rivaroxaban: N=6183 and Enoxaparin: N=6200) in the safety populations in these studies.

This report is concerned with evaluating signals of liver toxicity on data collected from the four RECORD studies. Safety is evaluated based on the results from tests conducted on blood specimens collected at specified time points from patients in each of the studies. As specified in the studies' protocols, liver assessment tests were to be performed on blood collected from all patients prior to surgery, on day of surgery (after surgery prior to treatment administration), and on 3 (RECORD 3 and 4) or 4 (RECORD 1 and 2) specified later occasions. Information on liver safety is also found in reports of liver-related adverse events occurring during the trials. These events are defined as those in the “Hepatobiliary Disorders” system organ class (SOC) in the MedDRA classification system.

## 2 INTRODUCTION

### 2.1 Objective

The objective of this report is to examine signals of liver toxicity by comparing the responses to treatment in patients undergoing short-term (2-5 weeks) treatment using Rivaroxaban (Xarelto) and those receiving Enoxaparin (Lovenox) as the control. The relevant data were collected from four Phase 3 studies, conducted by the sponsor. This evaluation will assess liver toxicity, primarily by focusing on liver assessment tests performed on blood specimens obtained from patients in these studies. In addition, it will also discuss reported adverse events related to the liver such as cases of jaundice and other hepatic disorders.

## 2.2 Background

Evidence of liver injury that is potentially drug-induced is seen in elevated levels of enzymes such as alanine aminotransferase (ALT) aspartate aminotransferase (AST), and alkaline phosphatase (ALP) and in total bilirubin (TBL). Patients whose lab tests demonstrate levels of ALT, AST, ALP, or TBL several times above the upper limit of normal (ULN) are therefore of particular interest in evaluating liver safety[1]. Rare patient deaths in the Phase 2 and Phase 3 clinical trials of Rivararoxaban, while not conclusively linked to the drug have raised the issue of liver toxicity with this NDA. In addition, anticoagulants (the class of drug which includes Rivaroxaban) have been associated with hepatotoxicity in the past.[2]

## 2.3 Experimental Design

All four RECORD studies were randomized, double-blind studies using Enoxaparin as the active control. These studies all included men and women, aged 18 years old and over. As Rivaroxaban is taken in tablet form and Enoxaparin as an injection, all patients randomized to the Rivaroxaban treatment arm received placebo injections during the treatment period of the study. Similarly, patients in the Enoxaparin arm received placebo tablets.

In all studies, screening and randomization occurred at baseline. The first dose of Enoxaparin was given 12 hours prior to surgery. Patients received 40mg daily of Enoxaparin in RECORD 1, 2, and 3 or 30mg twice daily in RECORD 4. The first dose of Rivaroxaban was given 6 to 8 hours after surgery. Patients receiving Rivaroxaban received 10mg daily in all RECORD studies. Treatment lasted for 35(± 4) days in RECORD 1, and 12 (± 2) days in RECORD 3 and RECORD 4. In RECORD 2, patients receiving Rivaroxaban were treated for 35 (± 4) days, while Enoxaparin patients were treated for 12 (± 2) days (followed by a period during which they received a placebo). The follow-up period in all studies lasted for 30 days.

The RECORD studies were not specifically designed to address liver safety, although liver safety is the focus of this report. The primary efficacy endpoint in these studies was a composite endpoint of any DVT, non-fatal PE, and death from all causes. The primary safety endpoint was incidence of treatment-emergent major bleeding observed no later than 2 days past the end of treatment. Analysis regarding which patients experienced the efficacy and bleeding endpoints is available in other reviews of this NDA.

The safety population consists of those patients randomized to receive either Rivaroxaban or Enoxaparin who received at least one blinded dose of their intended medication. The safety population includes 6,183 patients who received Rivaroxaban and 6,200 patients who received Enoxaparin. The proportion of randomized patients included in the safety population is nearly identical across the two treatment groups. This proportion does not vary largely across the four

[1] FDA Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation 2007. Available at http:www fda.gov/cder/guidance/7507dft.pdf

[2] Arora, Nipun, Goldhaber, Samuel Z. Anticoagulants and Transaminase Elevation. Circulation 2006; 113(15):e698-e702.

studies and ranges from 96.4% in RECORD 4 to 97.9% in RECORD 2. All analysis in this report is restricted to patients in the safety population. The distribution of these patients according to study and treatment is shown in Table 1.

Table 1. Distribution of Patients in Safety Population by Treatment Groups and Study

| Study | Rivaroxaban | Enoxaparin | Total | Surgery Type |
|---|---|---|---|---|
| RECORD 1 | 2209 | 2234 | 4433 | Hip Replacement |
| RECORD 2 | 1228 | 1229 | 2457 | Hip Replacement |
| RECORD 3 | 1220 | 1239 | 2459 | Knee Replacement |
| RECORD 4 | 1526 | 1508 | 3034 | Knee Replacement |
| Total | 6183 | 6200 | 12383 | |

Patients with "significant liver disease" were excluded from all four studies. Examples of relevant diseases include acute clinical hepatitis, chronic hepatitis, and cirrhosis. Liver assessment tests were included as part of the clinical chemistry laboratory evaluations performed on blood specimens collected from each patient. Relevant tests for this review include tests of AST, ALT, ALP, and TBL. Baseline values were obtained from samples collected up to two weeks prior to surgery. Tests were also performed on blood samples collected on: the day of surgery (day 1) between completion of surgery and the first scheduled dose of Rivaroxaban (or tablet placebo); on day 6 (± 2 days); and day 13 (± 2 days) in all RECORD studies. The protocols for RECORD 1 and 2 called for additional testing on day 36 (± 4 days) and day 65 (± 5 days), while RECORD 3 and 4 required a set of tests on day 42 (± 5 days).

Additional testing was required in the case of abnormal results. In the early post-operative period, defined as up to day 13 in all studies, patients with an ALT elevation above 5 times the ULN were to be retested within three days. If the patient's ALT level appeared to be returning to normal, tests were to be performed weekly until ALT fell below 2 times the ULN then every 2 weeks in the first 2 months then monthly until the ALT level returned to normal or its baseline value. If the ALT level appeared to be increasing, the patient was to be monitored daily until ALT fell below 2 times the ULN then every 2 weeks in the first 2 months then monthly until the ALT level returned to normal or its baseline value. Monitoring was not to be discontinued until two sets of tests indicated normal or near-baseline ALT levels.

Beyond day 13 (late post-operative period), the extended monitoring schedule described in the previous paragraph was to be instituted for patients with ALT above 3 (instead of 5) times the upper limit of normal.

Stopping rules relating to liver assessment tests were specified in all four studies. The study protocols also defined additional liver monitoring schedules for patients meeting the stopping criteria. Treatment was to be discontinued in the following cases:

• **ALL studies:** Jaundice or other clinical symptom of liver injury, in association with abnormal laboratory results.
• **ALL studies:** ALT levels above 4 times the ULN for more than 4 weeks.
• **ALL studies:** ALT levels above 3 times the ULN along with TBL above 2 times the ULN and a ratio of direct to indirect bilirubin greater than or equal to 50%.

• **ALL studies:** ALT levels above 8 times the ULN (confirmed within 3 days) in the early post-operative period
• **RECORD 1 and 2 only:** ALT levels above 5 times the ULN (confirmed within 3 days) in the late post-operative period. Also, when ALT was between 3 and 5 times the ULN with an increase of at least 1 ULN when patient was retested (within 3 days).

# 3. EVALUATION

Our assessment is based on the combined data from all four RECORD studies. This is consistent with previous discussions between the sponsor and FDA[3]. Our evaluation of the submitted data shows that the signals regarding liver safety were consistent across studies, indicating that no study effect was observed in the data. Such consistency provides justification for basing our analysis on the aggregated data.

We evaluate treatment effects by comparing peak enzyme and bilirubin levels observed in blood samples obtained from each patient on day 2 or later of the study. Note that many patients exhibit their highest enzyme and bilirubin levels on the day of surgery (day 1), but these elevations occur before Rivaroxaban patients begin treatment and may be due to surgery itself.

As described in the FDA's guidance on drug-induced liver injury, an elevated level of ALT measured in a patient's blood is a sensitive but not specific indicator of hepatocellular injury. Hepatocellular injury may also be observed through an elevated AST level, but this signal of potential injury is not as specific to the liver. An elevated level of bilirubin is a specific but not sensitive indicator of impaired liver function. Patients whose peak ALT levels (following exposure to the drug) are at least 3 times the ULN and whose peak TBL levels are at least 2 times the ULN meet two of the criteria for characterization as "Hy's Law" cases. Hy's Law patients are believed to have an increased risk of liver failure.

## 3.1 Laboratory Test Values

According to the study protocols, blood specimens taken on day 1 were obtained after surgery, but prior to the first post-surgery dose of the randomized treatment. For this reason, this report's analysis of peak enzyme and bilirubin levels only considers test results obtained from day 2 onward. Note, however, that patients randomized to the Enoxaparin group received their first dose prior to surgery; Rivaroxaban patients received their first dose on day1 after surgery and after the scheduled blood tests.

The joint distribution of peak ALT and TBL levels in patients from the four RECORD studies are shown, separated by treatment group, in Tables 2a and 2b. Frequencies in cells corresponding to ALT and TBL values in the Hy's Law range are bolded. We provide an in-depth discussion of possible Hy's Law cases in Sec 3.2. Note that the number of patients in the Rivaroxaban and Enoxaparin groups does not add up to 6,183 and 6,200 since information on liver assessment test results following surgery is not available for all patients.

[3] Pre-NDA meeting, December 13, 2007

| Table 2a. Peak Post-baseline Levels of ALT and TBL in Rivaroxaban Patients* | | | | | | |
|---|---|---|---|---|---|---|
| | Peak TBL (x ULN) | | | | | |
| Peak ALT (xULN) | 0 to <1 | 1 to <2 | 2 to <2.5 | 2.5 to < 3 | >=3 | total |
| 0 to <1 | 4253 | 263 | 6 | 1 | 1 | 4524 |
| | (70.7) | (4.4) | (0.1) | (0.0) | (0.0) | (74.2) |
| 1 to <2 | 1047 | 91 | 3 | 0 | 0 | 1141 |
| | (17.4) | (1.5) | (0.0) | (0.0) | (0.0) | (19.0) |
| 2 to <3 | 204 | 23 | 2 | 0 | 0 | 229 |
| | (3.4) | (0.4) | (0.0) | (0.00) | (0.00) | (3.8) |
| 3 to <5 | 70 | 8 | **1** | **0** | **1** | 80 |
| | (1.2) | (0.1) | **(0.0)** | **(0.0)** | **(0.0)** | (1.3) |
| 5 to <10 | 23 | 8 | **2** | **0** | **1** | 34 |
| | (0.4) | (0.1) | **(0.0)** | **(0.0)** | **(0.0)** | (0.6) |
| >=10 | 3 | 3 | **0** | **1** | **2** | 9 |
| | (0.0) | (0.0) | **(0.0)** | **(0.0)** | **(0.0)** | (0.1) |
| total | 5600 | 396 | 14 | 2 | 5 | 6017 |
| | (93.1) | (10.8) | (0.2) | (0.1) | (0.1) | (100%) |

***Numbers in parentheses reflect the percentage of patients in each cell***

| Table 2b. Peak Post-baseline Levels of ALT and TBL Enoxaparin* | | | | | | |
|---|---|---|---|---|---|---|
| | Peak TBL (x ULN) | | | | | |
| Peak ALT (xULN) | 0 to <1 | 1 to <2 | 2 to <2.5 | 2.5 to < 3 | >=3 | total |
| 0 to <1 | 3583 | 190 | 8 | 0 | 1 | 3782 |
| | (59.7) | (3.2) | (0.1) | (0.0) | (0.0) | (63.0) |
| 1 to <2 | 1528 | 118 | 6 | 2 | 1 | 1655 |
| | (25.4) | (2.0) | (0.1) | (0.0) | (0.0) | (27.6) |
| 2 to <3 | 337 | 25 | 1 | 1 | 1 | 365 |
| | (5.6) | (0.4) | (0.0) | (0.0) | (0.0) | (6.1) |
| 3 to <5 | 113 | 13 | **1** | **1** | **2** | 130 |
| | (1.9) | (0.2) | **(0.0)** | **(0.0)** | **(0.0)** | (2.3) |
| 5 to <10 | 51 | 8 | **2** | **0** | **1** | 62 |
| | (0.8) | (0.1) | **(0.0)** | **(0.0)** | **(0.0)** | (1.0) |
| >=10 | 3 | 3 | **0** | **0** | **3** | 9 |
| | (0.0) | (0.0) | **(0.0)** | **(0.0)** | **(0.0)** | (0.1) |
| total | 5615 | 357 | 18 | 4 | 9 | 6003 |
| | (93.5) | (6.0) | (0.3) | (0.1) | (0.2) | (100) |

***Numbers in parentheses reflect the percentage of patients in each cell***

As can be seen in tables 2a and 2b, the proportion of patients falling into each range of TBL values is comparable for the two treatment groups. As for ALT, a larger proportion of patients in the Rivaroxaban group have peak ALT values that fall the normal range in than in the Enoxaparin group. Comparisons between the two treatment groups do not show any markedly different trends when each RECORD study is examined separately. The similarity of the distribution of TBL values and the difference in the distribution of ALT values across treatment groups are further seen in the cumulative distributions of peak post-baseline ALT and TBL by treatment group as discussed in Appendix 1.

Tables 2a and 2b indicate that 8 patients in the Rivaroxaban group and 10 in the Enoxaparin group have peak post-baseline ALT and TBL levels in the Hy's Law range. An additional 2 Rivaraxoban patients had ALT or TBL levels in the necessary ranges at baseline. While these liver assessment test results cannot have been caused by Rivaraxoban, we include these patients in our preliminary count of study subjects with test results in the Hy's Law range.

There were 90 patients (40 Rivaroxaban, 50 Enoxaparin) with elevated ALT at baseline. Sixty-one patients (33 Rivaroxaban, 28 Enoxaparin) had elevated TBL at baseline. An additional two Rivaroxaban patients had elevated baseline levels for both tests. By "elevated" in this section, we mean at least three times the ULN for ALT and at least twice the ULN for TBL. All patients with elevated baseline TBL had elevated levels on Day 1 (the day of surgery). The vast majority (84) of patients with elevated baseline ALT also had elevated levels on day 1; the rest did so sometime in the three days preceding surgery.

Twenty-two patients (9 Rivaroxaban, 13 Enoxaparin) with elevated ALT at baseline continued to have elevated ALT post-baseline. These patients constitute 7.3% of the 123 Rivaroxaban patients and 6.5% of the 201 Enoxaparin patients with elevated ALT levels post-baseline. Nine of these (3 Rivaroxaban, 6 Enoxaparin) had peak ALT levels that increased after baseline. Six patients (4 Rivaroxaban, 2 Enoxaparin) with elevated TBL at baseline continued to have elevated TBL post-baseline. These patients constitute 19.0% of the 21 Rivaroxaban patients and 6.5% of the 31 Enoxaparin patients with elevated TBL levels post-baseline. Three of these (2 Rivaroxaban, 1 Enoxaparin) had peak TBL levels that increased after baseline. There were two patients with elevated baseline ALT (one in each treatment group) and one (Enoxaparin) patient with elevated baseline TBL without any available post-baseline liver assessment test results.

As with ALT levels, a larger percentage of Rivaroxaban subjects than Enoxaparin subjects (67% versus 62%) have peak AST levels at or below the ULN. For each of the specified ranges of elevated AST levels, a smaller proportion of Rivaroxaban patients fall into each range.

Table 3. Peak post-baseline levels of AST in Rivaroxaban and Enoxaparin patients. Numbers in parentheses reflect the percentage of patients in each cell

| Peak AST (xULN) | Rivaroxaban ALL RECORD STUDIES | Enoxaparin ALL RECORD STUDIES |
|---|---|---|
| 0 to <1 | 4544 (75.5) | 3926 (65.4) |
| 1 to <2 | 1209 (20.1) | 1685 (28.1) |
| 2 to <3 | 170 (2.8) | 259 (4.3) |
| 3 to <5 | 72 (1.2) | 96 (1.6) |
| 5 to <10 | 16 (0.3) | 30 (0.5) |
| >=10 | 7 (0.1) | 8 (0.1) |
| Total | 6018 (100) | 6004 (100) |

Table 4 - below – shows peak ALP levels for both groups. As seen in this table, a smaller percentage of Rivaroxaban subjects than Enoxaparin subjects (3.8% versus 5.1%) have peak ALP levels at or above 1.5 times the ULN.

| Table 4. Peak post-baseline levels of AST in Rivaroxaban and Enoxaparin patients. Numbers in parentheses reflect the percentage of patients in each cell | | |
|---|---|---|
| Peak ALP (xULN) | Rivaroxaban ALL RECORD STUDIES | Enoxaparin ALL RECORD STUDIES |
| 0 to <1.5 | 5786 (96.1) | 5690 (94.7) |
| >=1.5 | 234 (3.9) | 317 (5.3) |
| Total | 6020 (100) | 6007 (100) |

## 3.2 Hy's Law Patients

The number of patients with elevated levels of ALT and TBL that cannot be attributed to causes other than the drug is considered to be an important measure of a drug's potential for causing drug-induced liver injury. The patients meeting these criteria are known as Hy's Law Cases. Patients are not considered Hy's Law cases if they have ALP levels above two times the upper limit of normal. While such levels are unhealthy, they suggest that the patient may be suffering from cholestasis rather than hepatocellular injury and are thus do not face as large a risk for liver failure.[4]

To identify potential Hy's Law cases, we begin by identifying patients with peak ALT values above 3 times the ULN and peak TBL levels above 2 times the ULN at any point in the clinical trials. There are 10 patients meeting these criteria in each treatment group. We also consider expanded criteria of potential Hy's Law cases and count patients with peak TBL only 1.5 times the ULN. Similarly, we consider limiting our criteria and counting only patients with concurrent elevated ALT and TBL levels. The number of potential Hy's Law cases using different criteria is shown in Table 5.

| Table 5. Number (percentage) of potential Hy's law cases, using different criteria. Bolded criteria are those used for the purposes of this study. | | |
|---|---|---|
| Criteria | Rivaroxaban | Enoxaparin |
| ALT>3xULN, TBL>2xULN, concurrent | 9 (0.14) | 8 (0.13) |
| **Peak ALT>3xULN, peak TBL>2xULN** | **10 (0.16)** | **10 (0.16)** |
| ALT>3xULN, TBL>1.5 xULN, concurrent | 15 (0.24) | 12 (0.19) |
| Peak ALT>3xULN, peak TBL>1.5 xULN | 20 (0.31) | 18 (0.28) |

Starting from the 20 patients with peak ALT above 3 times the ULN and peak TBL above twice the ULN, we further examine which patients may be excluded as Hy's Law cases. We identify 4 Rivaroxaban patients and 2 Enoxparin patients with peak ALP levels above twice the ULN. These patients could therefore be potentially excluded. One of these 4 Rivaroxaban patients (ID 11357/540017029) first experienced TBL above 2 times the ULN on the day of surgery, prior to

[4] FDA Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation 2007. Available at http:www fda.gov/cder/guidance/7507dft.pdf

the first dose of medication. While this patient continued to have elevated TBL on days 6 and 11, his TBL levels decreased during that time.

One Rivaroxaban patient (ID 11355/600095028) only met the criteria for elevated ALT and TBL on day 55. This was nearly two weeks after the end of the 30-day follow-up period for this patient. An additional two patients (not counting the patient mentioned with high peak ALP) in each treatment group first experienced ALT above 3 times the ULN or TBL above the 2 times the ULN on or before the day of surgery. The designation of these patients as Hy's Law cases may also be in doubt. Although the first dose of Enoxaparin was administered on the day before surgery, elevations in ALT or TBL observed immediately after surgery may have been due to surgery itself rather than Enoxaparin.

The sponsor defines potential Hy's law cases as patients with concurrent (not peak) ALT levels above 3 times the ULN and TBL levels above 2 times the ULN. They therefore consider only 17 patients. After excluding the patient with the elevated ALT and TBL levels on day 55, 16 patients qualified for evaluation by a Liver Advisory Panel (LAP). Fifteen patients (8 Rivaroxaban, 7 Enoxaparin) were assessed by one, two, or three members of the four-member panel. One patient (in the Rivaroxaban group) was not assessed at all. Of the Rivaraxoban patients, 2 were considered to have ALT and TBL levels unrelated or unlikely to be related by the drug, and 5 were considered to have ALT and TBL levels possibly or probably related to the drug. There was a disagreement between panel members regarding an eighth patient. In the Enoxaparin group, 4 patients' ALT and TBL levels were considered to be unrelated or unlikely to be related to treatment. ALT and TBL levels in 3 patients were considered to be possibly or probably related to treatment.

When conducting their assessments, the LAP members did not know which drug a patient received. They therefore also did not know whether the patients first received their drug before or after the blood tests performed on day 1. Accordingly, when deeming ALT and TBL levels to be "possibly related" to treatment based on peak values obtained from these blood tests, they note that this designation is only valid if the patient was receiving Enoxaparin. A Rivaroxaban patient (ID 11357/540017029) is the only patient whose adjudication is affected by this issue.

An overview of the distribution of potential Hy's law cases according to their LAP adjudication status is shown in Tables 6a and 6b. These tables also indicate the number of cases that we might exclude due to timing or high peak ALP. Note that the majority of cases deemed by the LAP to have elevated ALT and TBL possibly due to the treatment drug also have elevated ALP.

| Table 6a. Potential Hy's Law cases in the Rivaroxaban group, by possible exclusions and LAP adjudication | | | | |
|---|---|---|---|---|
| | Exclusions according to timing or ALP | | | |
| Adjudication by LAP: | Peak ALT or TBL too early or too late | ALP>=2 x ULN | Neither | Total |
| Not adjudicated | 1 | 0 | 1 | 2 |
| Possibly/probably related/split decision | 1* | 3 | 2** | 6 |
| Not/unlikely related | 2 | 0 | 0 | 2 |
| Total | 4 | 3 | 3 | 10 |

*This patient had TBL over 6 times the ULN prior to receiving Rivaroxaban. He had peak ALP over twice the ULN and ALT over three times the ULN on day 11.
** Includes one patient whose ALT and TBL levels one panel member thought were possibly related and two thought were unrelated.

| Table 6b. Potential Hy's Law cases in the Enoxaparin group, by possible exclusions and LAP adjudication | | | | |
|---|---|---|---|---|
| | Exclusions according to timing or ALP | | | |
| Adjudication by LAP: | Peak ALT or TBL too early or too late | ALP>=2 x ULN | Neither | Total |
| Not adjudicated | 1 | 0 | 2 | 3 |
| Possibly/probably related/split decision | 1 | 1 | 1 | 3 |
| Not/unlikely related | 0 | 1 | 3 | 4 |
| Total | 2 | 2 | 6 | 10 |

### 3.3 Adverse Events in the "Investigations" SOC Among Potential Hy's Law Cases

Abnormal test results are reported as adverse events in the "Investigations" system organ class (SOC) in MedDRA. Of the 20 patients with peak ALT above 3 times the ULN and peak TBL above twice the ULN, 9 patients have at least one report of elevated ALT and at least one report of elevated TBL. Another 3 only have reports of elevated ALT. Of the 8 patients with no reports of elevated TBL or ALT, 7 had entries with the less specific designations "Hepatic enzyme increased" or "Liver function test abnormal." This suggests that the dataset containing laboratory test result for patients in the RECORD studies is much more informative regarding abnormal liver assessment test results than the dataset containing reports of adverse events.

The adverse events dataset indicates whether investigators and clinicians involved in the RECORD studies considered those abnormal test results reported as adverse events to be related to treatment. The information, however, is not consistent with the provided results on adjudication by the LAP. For example, two Rivaroxaban patients (ID numbers 11357/540017029 11355/140205040) have reports of elevated ALT and TBL that are both deemed "not related" to the drug, but the LAP considered this patient to "possibly" have ALT and TBL levels caused by the drug. In addition, the Rivaroxaban patient (ID 11357/550037007) whom two out of three LAP members considered not to have ALT and TBL levels caused by the drug, has adverse event listings for elevated ALT and TBL that are both classified as "possibly related".

### 3.4 Adverse Events in "Hepatobiliary Disorders" SOC Among Potential Hy's Law Cases

There were 9 hepatobiliary adverse events in 4 patients among the 20 potential Hy's Law cases. All events were reported as resolved.

One Rivaroxaban patient had two reports of jaundice and one report each of ocular icterus and hepatomegaly. None of these were serious. In the Enoxaparin group, one patient had a serious case of cholelithiasis, and another had reports of both serious cholelithiasis and cholecystitis. A third patient had two reports of "hepatic function abnormal", neither characterized as serious.

### 3.5 Hepatobiliary Adverse Events in the General Patient Population

Adverse events (AEs) in the RECORD studies were coded using the MedDRA dictionary, version 10.0. There were 80 adverse events in the four studies that are associated with the "Hepatobiliary disorders" system organ class (SOC). All but 17 of these have "Hepatobiliary disorders" as their primary SOC. These events do not include abnormal test results which can be found in the "Investigations" SOC in the MedDRA classification system or which can be identified in the dataset containing laboratory test results. The 80 events occurred in 67 unique patients, 28 of whom received Rivaroxaban and 39 of whom received Enoxaparin.

Table 7 displays the number of adverse events and serious adverse events, by treatment group. These events are aggregated by high level group term (HLGT). A list of events at the preferred-term level is shown in Appendix 3.

Table 7. Liver-related adverse events, by high level group term.

| | Rivaroxaban | | Enoxaparin | |
|---|---|---|---|---|
| | Total | Serious | Total | Serious |
| Bile Duct Disorders | 3 | 1 | 0 | 0 |
| Gallbladder Disorders | 7 | 2 | 16 | 7 |
| Hepatic and Hepatobiliary Disorders | 24 | 5 | 23 | 2 |
| Hepatobiliary Neoplasms | 1 | 0 | 0 | 0 |
| All | 35 | 8 | 45 | 9 |

Serious events in the Rivaroxaban patient population included three patients with jaundice and one with ascites. None of these discontinued treatment. Two patients had cases of acute cholecystitis, one of whom discontinued treatment. One patient with hepatic failure and one with cholangitis also discontinued treatment. These eight events occurred in eight unique patients, none of whom were potential Hy's Law patients.

In the Enoxaparin group, nine serious hepatobiliary adverse events occurred in seven patients. Two patients had serious cases of both cholecystitis and cholelithiasis. One of these was also a potential Hy's Law case and discontinued treatment. Another two patients had serious cases of cholecystitis, and one of these discontinued treatment as well. Two patients had serious cases of hepatitis; one discontinued treatment, while one did not. Lastly, a patient with cholelithiasis (a potential Hy's Law case) did not discontinue treatment.

### 3.6 Hepatobiliary Adverse Events in Patients Who Died During the Clinical Trials

There were 14 patients in the Rivaroxaban group and 25 patients in the Enoxaparin group who died during the four RECORD studies. Of these, three had adverse events in the hepatobiliary SOC. None were serious. One of these was a patient in the Enoxaparin group with Hypoalbuminaemia. This event was resolved prior to the patient's death. Another patient in the Enoxaparin group had cases of porcelain gallbladder and gallbladder disorder. These were also resolved prior to the patient's death. Lastly, there was a patient in the Rivaroxaban treatment group with two entries for cholelithiases. This condition was never resolved.

### 3.7 Data Quality and Adherence to Monitoring Schedule

Protocols for all four RECORD studies indicate that blood specimens for liver assessment tests be obtained for all patients in all studies on 4 occasions: during the two weeks prior to surgery; on the day of surgery, after surgery but before the first dose of medication; on day 6 (± 2 days); and on day 13 (± 2 days). The protocols for RECORD 1 and 2 called for additional testing on day 36 (± 4 days) and day 65 (± 5 days), while RECORD 3 and 4 required a set of tests on day 42 (± 5 days). Table 8 illustrates what percentage of patients had liver assessment test results available for each of the required tests.

Table 8. Adherence to monitoring schedule, by day of test and study

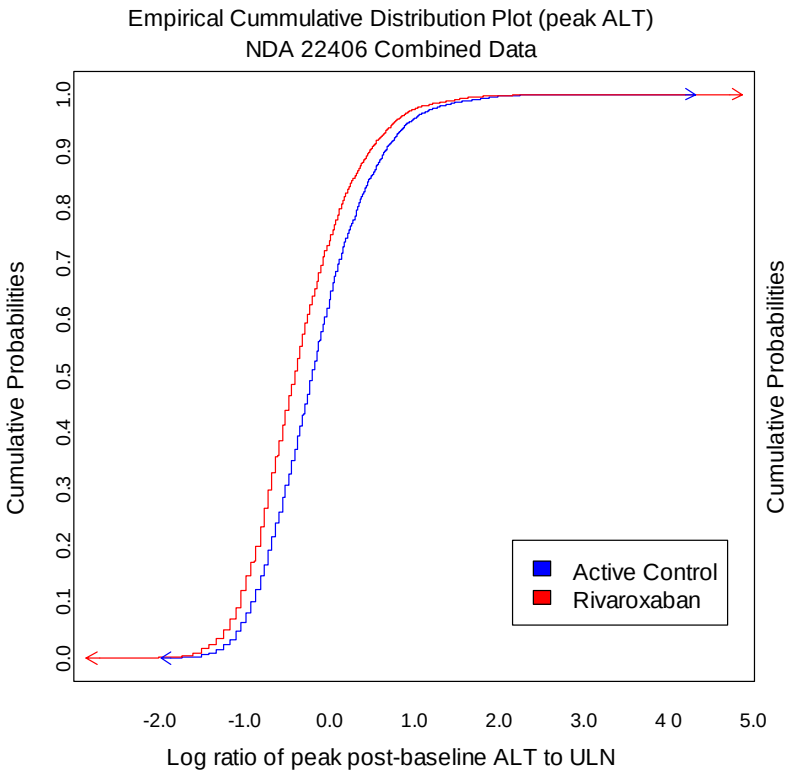
| | RECORD 1 | RECORD 2 | RECORD 3 | RECORD 4 |
|---|---|---|---|---|
| Before surgery | 98.0 | 97.2 | 97.2 | 89.8 |
| Day of Surgery (Day 1) | 97.4 | 95.2 | 95.3 | 97.3 |
| Day 6±2 | 85.3 | 84.6 | 93.0 | 94.2 |
| Day 13±2 | 86.5 | 89.0 | 84.2 | 88.7 |
| Day 36±4 | 85.2 | 86.0 | N/A | N/A |
| Day 42±5 | N/A | N/A | 74.0 | 81.6 |
| Day 65±5 | 73.1 | 78.1 | N/A | N/A |

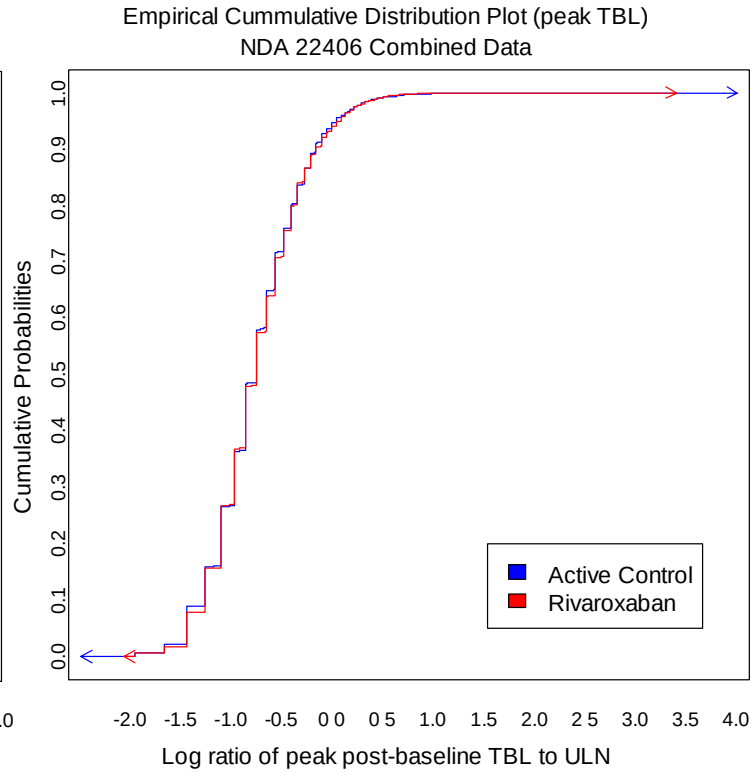
# 4. SUMMARY AND CONCLUSIONS

We began by evaluating signals of liver toxicity in liver assessment test results from patients in the Rivaraxoban and Enoxaparin treatment groups. We find that Rivaraxoban patients have lower peak post-baseline levels of ALT, AST, and ALP than Enoxaparin patients. TBL levels are comparable in the two groups. We discussed which patients could be considered Hy's Law cases, that is, those patients who are at particular risk of liver failure. While counting Hy's Law patients can be a subjective endeavor, there does not appear to be a larger number of these patients in the Rivaraxoban group. In addition, there are fewer total and serious adverse events in the hepatobiliary SOC among Rivaraxoban patients than among Enoxaparin patients.

## Appendix 1: Cumulative Distribution of ALT and TBL

The two figures below illustrate the cumulative distributions of peak, post-baseline ALT and TBL respectively. In the first figure, values of the log of the ratio of ALT to the ULN appear on the x-axis, while on the y-axis are probabilities that a randomly selected observation is below the values on the x-axis. The line corresponding to the distribution of ALT values in the Rivaroxaban group is consistently above the line representing the Enoxaparin group; this means that, for any ratio of ALT to the ULN, a larger proportion of observations in the Rivaroxaban group fall below that value. In other words, peak ALT values are generally lower in the Rivaroxaban group. In Figure 2, depicting the distributions of peak TBL, the two lines more or less overlap. This indicates that the distribution of peak TBL values does not noticeably differ by treatment group.



## Appendix 2: Adverse Events, by MedDRA Preferred Term

| Liver-related Adverse Events | | |
|---|---|---|
| | Rivaroxaban | Enoxaparin |
| **Bile Duct Disorders:** | | |
| Biliary Colic | 1 | 0 |
| Biliary Dilation | 1 | 0 |
| Cholangitis | 1 | 0 |
| **Total** | **3** | **0** |
| **Gallbladder Disorders** | | |
| Cholecystitis | 1 | 5 |
| Cholecystitis acute | 2 | 0 |
| Cholecystitis chronic | 0 | 1 |
| Cholelithiasis | 2 | 8 |
| Gallbladder disorder | 1 | 1 |
| Gallbladder pain | 1 | 0 |
| Porcelain gallbladder | 0 | 1 |
| **Total** | **7** | **16** |
| **Hepatic and Hepatobiliary Disorders** | | |
| Ascites | 2 | 0 |
| Cholestatis | 1 | 0 |
| Cytolytic hepatitis | 1 | 0 |
| Hepatic failure | 1 | 0 |
| Hepatic function abnormal | 3 | 6 |
| Hepatic lesion | 0 | 2 |
| Hepatic steatosis | 3 | 2 |
| Hepatitis | 0 | 2 |
| Hepatitis B | 1 | 1 |
| Hepatomegaly | 1 | 1 |
| Hepatotoxicity | 0 | 1 |
| Hyperbilirubinaemia | 1 | 4 |
| Hypoalbuminaemia | 2 | 8 |
| Hypoproteinaemia | 0 | 1 |
| Jaundice | 6 | 1 |
| Ocular icterus | 1 | 0 |
| Varices oesophageal | 1 | 0 |
| **Total** | **24** | **29** |
| **Hepatobiliary neoplasms** | | |
| Hepatic cyst | 1 | 0 |
| **Total** | **1** | **0** |
| **All** | **35** | **45** |

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